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Disease-a-Month

External Manifestations of Internal Disease

HARVEY ROTHBERG
HAROLD JEGHERS

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External Manifestations of Internal Disease

HARVEY ROTHBERG
HAROLD JEGHERS

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Harvey Rothberg

is Clinical Instructor of Medicine at Seton Hall College of Medicine. A graduate of Harvard Medical School, he trained in medicine at the Massachusetts General Hospital and in hematology at Walter Reed Army Institute of Research. His special interests include hematology and neoplastic disease. He has published papers on leukemia therapy, spleen functions and bone marrow treatment of radiation injury.

Harold Jeghers

is Professor and Director of the Department of Medicine at Seton Hall College of Medicine. A graduate of Western Reserve University School of Medicine, he trained at the Boston City Hospital, where he became Chief of the Fifth Medical Service and Associate Professor of Medicine at Boston University School of Medicine. From 1946 to 1956 he was Professor of Medicine at Georgetown University School of Medicine. His special interests include pigmentation of the skin, nutrition, gastroenterology and medical education.

SINCE ANCIENT TIMES, physicians have been aware of the value of external signs as clues to the presence and nature of systemic disease. However, in an age of increasing reliance on laboratory studies, this concept appears deserving of restatement. This review is confined to those features of the physical examination which can be comprehended by simple inspection, and it emphasizes certain aspects of diagnostic medicine which may not be widely known. In general, we have omitted conditions that are primarily of dermatologic interest or local origin. For the most part, we have also omitted consideration of neurologic signs and symptoms. No apology is made for the inclusion of a number of rare entities, since diagnosis of obscure disease is best made by the prepared mind, and differential diagnosis of common diseases should involve exclusion of the unusual.

I. REGIONAL INSPECTION

Body Build

While the concept of constitutional susceptibility to specific diseases is of limited diagnostic value, certain generalizations can be made. For example, the typical young patient with coronary heart disease is a male who is an endomorphic mesomorph; he is basically of muscular and large-boned build but with a tendency to roundness and overweight (26). Obesity strongly predisposes to diabetes, atherosclerosis, degenerative joint disease and gallstones and is associated with excess mortality from hypertension, coronary artery disease and even cirrhosis of the liver. Extreme obesity may lead to alveolar hypoventilation, somnolence and polycythemia.

Emaciation and *cachexia* may occur in any chronic debilitating disease, such as disseminated cancer or malnutrition. In emaciated young women, anorexia nervosa may be distinguished from hypopituitarism by the presence of axillary and pubic hair and normal breast tissue, and by the persistence of normal strength and activity despite bodily wasting. Women with hypopituitarism are thin but rarely emaciated.

Short stature is usually due to genetic and familial factors and is not pathologic. However, true *dwarfism* almost always indicates systemic disease during the childhood years of skeletal growth and maturation. Many cases of retarded growth are nonspecific and secondary to such factors as severe renal disease, congenital heart disease, malnutrition or chronic infection. Rickets and renal tubular defects interfere with endochondral bone formation and, in severe cases, may lead to dwarfism.

A more specific type of dwarfism is that of *endocrine* origin, as in cretinism or juvenile hypothyroidism; in prepubertal hypopituitarism, which results in the symmetrically developed but sexually infantile pituitary dwarf; or in sexual precocity with early epiphysial fusion as a result of excess androgen or estrogen. Patients with Turner's syndrome of gonadal dysgenesis usually attain a height of just under 5 feet and may be recognized by their sexual infantilism and frequently associated webbing of the neck and wide carrying angle of the arms. Delayed adolescence may also be considered an endocrine cause of retarded growth; but it is not an abnormality, and eventually these patients attain normal growth and development.

A third category of dwarfism is comprised of the primary *disorders of bone and cartilage formation.* (35). Most familiar is the achondroplastic dwarf, who is recognizable by his short extremities and relatively normal trunk. In contrast, in Morquio's disease both spine and extremities are short and the trunk is severely deformed. In gargoylism, or Hurler's syndrome, there are also grotesque deformities involving the head, trunk and extremities; but, in addition, there is progressive mucoprotein deposition which leads to hepatosplenomegaly, cardiac abnormality, corneal clouding and usually mental retardation. In severe osteogenesis imperfecta, multiple fractures may be the cause of short legs and a relatively large head, so that affected patients may superficially resemble achondroplastic dwarfs.

A fourth group consists of the *constitutional or primordial dwarfs.* Sporadic cases are very rare; there is a familial tendency, as in the Pygmy race of Central Africa. Finally, *progeria* results in a normally proportioned but prematurely aged, sexually retarded, wizened and emaciated little person, who typically dies of arteriosclerosis before the age of twenty.

Gigantism may result from prepubertal excess of pituitary growth hormone or from constitutional factors. The latter are usually familial, as in the descendants of the Watusi of East Africa. Patients with Marfan's syndrome are characterized more by their altered skeletal proportions than by the increased over-all height; they are rarely over 6½ feet tall (35). Similarly, the eunuchoid male has long extremities but a relatively short trunk, so that his over-all height is not greatly increased.

Another developmental disturbance which may be considered here is *situs inversus* (30). In males, this condition may be suspected by finding the right testis hanging lower than the left. While situs inversus itself is harmless, if unrecognized it may cause confusion in the diagnosis of unilateral visceral disease. Occasionally it is associated with other congenital anomalies, or with bronchiectasis and sinusitis (Kartagener's syndrome).

Skin

Diagnostic rashes: *Acute exanthems.*—The specific diagnostic rashes are too well known to merit detailed consideration. Perhaps most common are the multiple blotchy dark red maculopapules of *measles,* which usually start on the forehead or behind the ears and spread, after a day or two, to the rest of

the body. They are typically preceded by the appearance of Koplik spots and are associated with cough, coryza and conjunctivitis. The maculopapules of *rubella* are smaller and pinker and usually less elevated than those of measles and are characteristically associated with posterior cervical and occipital lymphadenitis. The rash sometimes seen in *ECHO virus* and *Coxsackie A virus* infections is quite variable, but tends to be maculopapular and generalized in infants and more rubelliform and limited to the face, neck and chest in older children and adults.

Rarely seen today are the lesions of *smallpox*—multiple papules which evolve simultaneously into umbilicated vesicles and finally pustules, involving especially the face, arms and trunk and extending to the palms and soles. They contrast with the familiar eruption of *chickenpox*, which consists of clear vesicles on an erythematous base, found in various stages of development and principally on the trunk and scalp.

Scarlet fever presents a diffuse bright erythema over the trunk, axillae, groin and inner aspects of the arms and thighs; it is typically associated with circumoral pallor, a coated tongue with swollen papillae (strawberry tongue), and pharyngitis. Characteristically the rash is followed during the second week by a branny desquamation of the affected skin. In *erysipelas*, there is marked erythema and edema of the skin with involvement of the superficial lymphatics, which causes a characteristic irregular but sharply demarcated margin which often fails to extend across bony prominences.

Syphilis, typhoid and the rickettsioses.—The generalized reddish-brown nonpruritic maculopapular eruption of secondary *syphilis*, extending over face and trunk and including palms and soles, is quite characteristic; however, syphilitic rashes may take other forms as well. The "rose spots" of *typhoid fever* are few in number and consist of small, round, slightly elevated maculopapules scattered over the upper abdomen and lower chest; these lesions are nonhemorrhagic and they blanch on pressure. In contrast, the maculopapular lesions of either *endemic* or *epidemic typhus* are widespread, occurring first on the trunk and later on the extremities, usually sparing the palms, soles and face; ultimately the lesions become hemorrhagic. In *Rocky Mountain spotted fever*, a rash similar to that of typhus appears first on the wrists, ankles and back and subsequently becomes generalized, usually extending to the palms,

soles and face. In *rickettsialpox*, there are scattered maculopapules which develop apical vesicles and thus mimic chickenpox; however, the latter disease differs in that the papules are entirely transformed into vesicles and there is no initial ulcerative eschar, such as occurs at the site of the mite bite in rickettsialpox.

Bacteremias.—Certain septicemic states may exhibit striking cutaneous manifestations. Most familiar are the multiple abscesses or furuncles that suggest *staphylococcal* infection. The generalized petechial or purpuric eruptions of acute or chronic *meningococcemia* are also well known. The skin lesions of *Pseudomonas* and other gram-negative bacteremias are being seen with increasing frequency. Typically they begin as large macules which progress to bullae or pustules, undergo a central slough and ultimately form a necrotic ulcerating lesion, the "ecthyma gangrenosum." The lesions are most common in the anogenital region but may occur anywhere (23).

Herpetic eruptions.—These eruptions are characterized by grouped, usually pruritic, vesicular lesions. *Herpes simplex* is usually perioral, occasionally genital or ocular; rarely does it occur in other sites. Exacerbations occur in many febrile states, including about a third of the cases of pneumococcal pneumonia. Sunlight, local trauma, menstruation and emotional upsets may also precipitate attacks. *Herpes zoster*, the adult form of chickenpox, is manifested by early pain followed by grouped vesicles on an erythematous base, in the distribution of a cranial or spinal nerve dermatome. While usually without systemic significance, this eruption is sometimes associated with Hodgkin's disease, lymphosarcoma or metastatic carcinoma. Occasionally herpes zoster produces, in addition to the dermatome patch, a generalized varicelliform eruption; this is most common in patients with chronic lymphatic leukemia.

Dermatitis herpetiformis is a chronic disorder with intensely pruritic lesions symmetrically grouped over trunk and extremities. Occasionally it is associated with visceral malignancy, especially after radiation therapy. *Herpes gestationis* is a variant of dermatitis herpetiformis which occurs during the latter half of pregnancy and is sometimes associated with stillbirths or fetal abnormalities.

The erythemas.—The erythemas form an interesting and often confusing group of disorders which often have both systemic and cutaneous manifestations. The term *toxic erythema*

refers to any generalized diffuse erythematous eruption, such as occurs in measles, scarlet fever, rubella and various other acute infections. Toxic erythema may also result from drug allergy.

Erythema multiforme is an acute symmetrical eruption thought to represent an allergic response to drugs or bacterial or viral infections. Usually there are few symptoms, but occasionally there is a systemic reaction with fever, malaise and arthralgia. As the name implies, the morphology is varied; but usually the lesions are macular or papular, and they occur predominantly on the dorsum of the hands and feet, the face and neck, the wrists and the lower legs. The lesions tend to expand peripherally and to clear centrally. When this pattern occurs in larger lesions, especially where there has been some ecchymosis, the characteristic "iris lesion" is produced. Vesicular or bullous lesions may occur in severe cases. Erythema multiforme is frequently associated with acute infections, with reactions to drugs (especially sulfonamides and penicillin) and occasionally with visceral malignancy.

Erythema marginatum is a variant of erythema multiforme often regarded as specific for rheumatic fever, although rarely it has been noted in other conditions. It consists of reddish maculopapular lesions which enlarge rapidly and clear centrally to form characteristic segments of circles which join or intersect to form scalloped or crescentic patterns.

Exudative erythema multiforme (Stevens-Johnson syndrome) is a more serious disorder, characterized by abrupt onset with fever, severe constitutional symptoms and denuded ulcerative mucosal lesions of mouth, conjunctiva and genitalia (41). Stomatitis is marked and may extend to involve pharynx and esophagus. Ocular lesions are serious and may progress to blindness. (The term Behçet's disease has been applied to cases which are recurrent and cyclical and in which the ocular involvement is prominent, especially where there is iritis with hypopyon.) Among the etiologic agents which have been implicated are the sulfonamides, penicillin and the viruses of herpes simplex, psittacosis and Asian influenza.

Reiter's syndrome has many of the features of exudative erythema multiforme, including oral mucosal lesions in many cases. However, the prominence of joint involvement plus the frequent occurrence of keratoderma blennorrhagica serve to set this syndrome apart as a separate entity. Pleuropneumonia-

like organisms and Shigella bacilli have been cultured in some cases.

The skin lesions of *erythema nodosum* are bright red, tender and painful nodules, 1–5 cm. in diameter, which usually appear on the extensor surfaces of both legs, but occasionally on the arms; they are commonly associated with low-grade fever, malaise and arthralgia. About 90% of cases occur in females. In most of the United States, a frequent cause is recent streptococcal infection; in the Southwest, coccidioidomycosis is commonly associated; and in Europe, tuberculosis is often found. Other associated diseases include ulcerative colitis, sarcoidosis, lymphogranuloma venereum, histoplasmosis, cat-scratch disease and allergy to drugs such as the sulfonamides or iodides.

Erythema induratum is a more chronic disorder consisting of deep subcutaneous nodules with red or purple discoloration of the overlying skin, the lesions appearing on the calves of the legs of young women. The lesions usually rise to the surface and ulcerate, but they may subside spontaneously. Histologically the lesions show the typical tubercles, caseation necrosis and, frequently, the organisms of tuberculosis.

Nodular vasculitis (5).—The lesions of nodular vasculitis are similar to those of erythema induratum except that they are smaller and usually do not ulcerate. They tend to occur in middle-aged women, and tubercle bacilli cannot be demonstrated. Systemic hypertension is frequently associated.

Weber-Christian disease, or relapsing febrile nonsuppurative panniculitis, is characterized by recurrent bouts of fever associated with crops of tender subcutaneous nodules of inflammation and necrosis in fatty tissue, with erythema of the overlying skin. The lesions are most common on the thighs, but they also occur on the lower legs, arms and trunk. The disease is most common in women between the ages 20 and 40, and it is frequently associated with fever, splenomegaly, leukopenia and anemia. Bouts of abdominal pain may occur, probably due to involvement of peripancreatic, perirenal and mesenteric fat deposits. The etiology of this disease and that of nodular vasculitis is unknown.

Endocarditis.—In subacute bacterial endocarditis, any of several cutaneous manifestations may occur. Pallor is usually evident, reflecting the anemia that is nearly always present. The finding of petechiae, sometimes with whitish centers, especially on the conjunctival or buccal mucosa, is often of diagnostic

value. Petechiae in the nail beds are likely to appear as splinter hemorrhages. Occasionally pustular lesions occur, particularly in staphylococcal endocarditis. Most specific are the Osler nodes —painful, tender, pea-sized reddish purple nodules which appear on the pads of the fingers or toes or on the palms, last 2 or 3 days and then disappear. They may have whitish centers and may be embolic in nature. Janeway's lesions, seen in both acute and subacute endocarditis, are small erythematous partially hemorrhagic nontender macular lesions, characteristically found on the palms and soles. These cutaneous manifestations of endocarditis are less commonly seen today than in the past, probably because of earlier diagnosis and specific therapy. The classically described "café-au-lait" skin is now a rarity in bacterial endocarditis.

Tuberculosis and sarcoidosis.—Still seen occasionally are tuberculous cervical adenitis (scrofula) and the gradually extending, soft nodular or crusted verrucous plaques of lupus vulgaris. Less common are erythema induratum, the papulonecrotic tuberculids and erythema nodosum due to tuberculosis.

Sarcoidosis may exhibit any of a variety of persistent papules, nodules or infiltrated plaques. Lesions on the face are most common, but they also occur on the extremities and trunk. Typically they are reddish blue to brown and do not ulcerate. Firm nodules at the interphalangeal joints are also characteristic. Biopsy is required for diagnosis. Recognition of the cutaneous manifestations of sarcoidosis may facilitate the diagnosis of obscure disease involving lungs, eyes, liver and spleen, kidneys, heart and other structures.

PALLOR.—Pallor may be evident on inspection of skin, tongue or mucous membranes. It is most often a sign of anemia, which occurs in a variety of illnesses, including blood loss, nutritional deficiency, hemolysis, marrow dysfunction and a host of chronic diseases. However, pallor may also result from vasoconstriction, such as occurs in medical or surgical shock; or in toxic states, including acute infections; or with autonomic changes, such as occur with fright or vomiting. Massive edema may cause diminution in skin color, as in the nephrotic syndrome. In hypothyroidism, pallor may result from the combination of anemia with mucinous edema and diminished blood flow in the skin. In scleroderma, pallor may result from the diminished vascularity of atrophic skin. The waxy pallor of pituitary insufficiency is disproportionate to the anemia; it results from diminished

melanization plus cutaneous vasoconstriction. Diminished melanin pigment is also responsible for the pallor of albinism, phenylketonuria and male hypogonadism.

PIGMENTATION.—Normal skin color is a composite produced by the presence of (*a*) carotene in the cornified epidermis, melanin and a related melanoid pigment primarily in the basal layers and to a lesser degree in the upper epidermis and (*b*) oxyhemoglobin and reduced hemoglobin within the interpapillary capillary loops and subpapillary vascular plexuses of the dermis (28). The color of the skin varies with racial differences in melanization, anatomic differences (e.g., mucous membrane as against skin), physiologic variations in blood flow and the optical phenomenon of scattering of light, whereby blue colors are reflected from pigment in the deep skin and red colors absorbed. Abnormal pigmentation may result from an excess of the normal pigments or from the presence of other pigments in the skin.

Increased *melanin pigmentation* (33) is commonly encountered. The pattern of increase is usually nonspecific, being accentuated in skin folds or areas of friction, such as the axillae or groins, between the buttocks and under the breasts. At times the pigmentation is generalized or accentuated in normally melanized areas. Only a few patterns of melanization are sufficiently distinctive to be diagnostic; these include acanthosis nigricans, the "raindrop" pigmentation of arsenic poisoning, the mucocutaneous pigmentation associated with small-bowel polyposis and the café au lait spots of neurofibromatosis and of Albright's syndrome. Any inflammatory lesion in the skin may be followed by local melanosis. Increased melanin pigmentation may also be due to genetic factors, endocrine changes, neurologic abnormalities, severe malnutrition, liver disease, old age and any chronic debilitating disease.

Yellow pigmentation most often results from *jaundice*. The color is due to excess bilirubin or its derivatives in the skin and may result from excess hemolysis, liver disease or biliary obstruction. The bilirubinophilia of elastic tissue accounts for the accentuation of yellow color in areas rich in this tissue, such as the scleras and the undersurface of the tongue. The lemon yellow color of the pernicious anemia patient results from the combination of pallor and mild jaundice due to hemolytic disease. A greenish jaundice, due to increased biliverdin, is suggestive of prolonged biliary obstruction.

Excess ingestion of foods that are rich in carotene may increase this normally present pigment so that it is clinically recognizable as *carotenemia.* In contrast with jaundice, the yellow color is accentuated in the areas of heaviest skin keratinization (the palms and soles) and greatest sebaceous activity (over the greasy parts of the face) and is absent from the sclerae or mucous membranes. Carotenemia also accounts for the yellow tint of myxedema and hypopituitarism. Rarely, lycopenemia, simulating carotenemia, may occur when excess tomatoes are consumed. The ingestion of certain yellow drugs, such as quinacrine, also produces a clinically detectable yellow color. In chronic uremia, retention of urochrome pigments may add a yellow tint to the skin.

Color changes due to hemoglobin abnormalities and to heavy metals are discussed below.

CYANOSIS.—Cyanosis normally is indicated by the bluish color of excessive amounts of reduced hemoglobin in the subpapillary venous plexus of the skin. Cyanosis is best noted in places where the skin is thin and not heavily melanized—e.g., the lips, ear lobes or nail beds. It is usually due to the entry of nonoxygenated blood into the systemic arterial circulation, such as occurs in congenital heart disease with a right to left shunt, or in pulmonary hemangiomatosis, or in bronchopneumonia with maintenance of circulation while there is impairment of ventilation in an involved segment of lung. The latter mechanism is also involved in the cyanosis of severe chronic pulmonary disease.

In certain instances, cyanosis may be peripheral in origin, owing to retarded blood flow through the skin and the resultant removal of more than the usual amount of oxygen from the circulating blood. This occurs in congestive failure and in severe shock. In shock, an ashen gray color may result from the combination of pallor and cyanosis. In polycythemia vera, arterial oxygen saturation is usually normal and cyanosis is due chiefly to the slow peripheral blood flow resulting from increased viscosity of the blood. At times cyanosis is localized, as in the acral cyanosis of peripheral vascular disease or the cyanosis of the head and neck in the patient with superior vena caval obstruction. Transient patchy cyanotic episodes are the hallmark of the metastatic carcinoid syndrome (46).

At times a variation in the hue of cyanosis may suggest a diagnosis. Patients with polycythemia vera often have a ruddy

cyanosis that contrasts with the dusky cyanosis of cardiac or pulmonary disease. Greenish cyanosis, from the combination of jaundice and cyanosis, is a classic sign of tricuspid stenosis, but it may occur with severe right heart failure of any etiology.

Cyanosis without either cardiorespiratory difficulty or clubbing may be the clue to a diagnosis of methemoglobinemia or sulfhemoglobinemia. In vitro, the former is a characteristic chocolate brown color, while the latter is mauve blue; however, distinction on the basis of skin color is not usually possible. Although clinically recognizable cyanosis usually requires 5 Gm. of reduced hemoglobin per 100 ml. of blood, only 1.5 Gm. of methemoglobin and less than 0.5 Gm. of sulfhemoglobin is required by most observers.

EDEMA.—Generalized edema is almost always an indication of systemic disease. However, local factors invariably help determine its distribution, as in dependent areas, where venous pressure is increased, or in lax tissues, such as the periorbital space, where tissue pressure is normally low. Immobilization of an extremity may cause localized edema in a normal person. Any of several mechanisms may lead to edema formation: increased permeability of capillaries, as in acute nephritis and allergic reactions; increased capillary blood pressure, as in venous obstruction or congestive failure; decreased plasma oncotic pressure, as in the hypoalbuminemia of cirrhosis, nephrotic syndrome or severe malnutrition; decreased tissue pressure, as in elderly persons or patients who have lost considerable weight; and renal retention of sodium and water, which must be present before significant generalized edema of any etiology can occur. Frequently there are multiple causes, as in the edema of congestive failure, liver disease or malnutrition. Ordinarily, several liters of fluid must be retained before edema can be detected on physical examination.

PURPURA.—Purpura, or extravasation of blood into skin and mucous membranes, may be a manifestation of a large number of systemic disorders. Vascular, extravascular and intravascular abnormalities must all be considered.

In many cases, the appearance of the lesion will suggest the diagnosis. Petechiae are minute in size, result from small extravasations in the interpapillary areas of the skin and are close enough to the surface so that their hemoglobin appears red. Ecchymoses represent more extensive bleeding from deeper subpapillary vessels and, because of the scattering phenomenon,

appear blue. Minute petechiae, especially on the legs, are the most characteristic manifestation of thrombocytopenia; however, patients with low platelet counts may exhibit larger ecchymotic spots, epistaxis, menorrhagia, hematuria or other hemorrhagic phenomena as well. Local factors play a definite role in determining the site of appearance of petechiae in the thrombocytopenic patient. This is shown by their normal occurrence in dependent areas, by the showers of petechiae in face and retina that may attend a bout of vomiting or by the linear streaks of petechiae that may indicate the trauma of a scratch.

Irregular bright red purpuric spots suggest a vascular component such as may occur in drug allergy, acute infections or Schönlein-Henoch purpura. In Schamberg's disease, capillary extravasations on the lower legs recur over many years and eventually lead to spotty yellowish-brown pigmentation. Perifollicular, gingival and subperiosteal hemorrhages are suggestive of scurvy.

Spontaneous ecchymoses and, to a lesser extent, hematuria are the most common manifestations of deficiencies of proconvertin and prothrombin such as occur with liver disease or anticoagulant therapy. Similar large extravasations in skin and mucous membranes are characteristic of the bleeding diathesis of uremia, even though the most consistent laboratory abnormality here is a qualitative defect in platelet function. Extensive deep hematomas, bleeding into the joints and excessive bleeding after trauma are suggestive of the hemophilioid diseases. Severe generalized purpura may indicate fibrinogenopenia, such as may result from massive intravascular coagulation (as in abruptio placentae or amniotic fluid embolism) or from the action of a fibrinolysin (as in certain patients with shock or carcinoma of prostate or pancreas).

The limited value of the above generalizations is evident. In addition to complete physical examination, the etiologic diagnosis of the purpuras usually requires a detailed history and meticulously performed laboratory studies.

PRURITUS.—Generalized pruritus without visible cutaneous lesions may herald or accompany the development of internal disease (43). A common cause of pruritus is simply dry skin, which results from the combination of diminished sweating and diminished sebaceous gland activity. Generalized pruritus occasionally occurs in early diabetes, in which a dry skin is very common. A more severe problem in some diabetic patients is pruri-

tus vulvae, which is usually attributable to moniliasis. In fact, localized pruritus in any area is unlikely to be due to systemic disease per se.

The association of pruritus and jaundice is familiar. However, there is no correlation between the level of bilirubin elevation and the presence or severity of itching. That pruritus is not related to jaundice per se but to biliary obstruction is indicated by its absence in hemolytic icterus and its almost universal presence in biliary cirrhosis. Pruritus occurs in about a third of the cases of common duct obstruction (whether by stone, stricture or neoplasm) but in only about 10% of patients with infectious hepatitis. Pruritus may be related to retention of bile salts, and it has been dramatically relieved by T-tube drainage in some cases.

Generalized pruritus may be a harbinger of malignant disease, either in the skin or internally or both. Mycosis fungoides and Hodgkin's disease are the most common neoplasms to present in this way (6, 31). In the former, there may be no visible lesion initially, but subsequently nonspecific scaling erythematous eruptions are succeeded by specific plaques and tumors. Occasionally the leukemias or lymphomas will present as pruritus, and rarely a carcinoma or sarcoma may do so. In the lymphocytic neoplasms, pruritus may be on the basis of infiltration of the skin.

Uremia is also frequently associated with severe generalized pruritus, which may be due to dryness of the skin plus retention of waste products. Pruritus occasionally occurs in polycythemia vera, particularly after a warm bath, which causes cutaneous vasodilatation. In the final months of pregnancy, an intense persistent pruritus occasionally develops without evidence of changes in the skin. The cause of the itching is unknown, but it quickly disappears after delivery.

Urticaria is usually short lived and is attributable to allergy to foods or drugs or to emotional factors. However, persistent urticaria may be a clue to the existence of an underlying systemic condition—for example, a gastrointestinal disorder, such as biliary tract disease and intestinal parasitism; chronic infection, especially by fungi; and malignant disease, especially with necrotic tumors or the lymphomas. The triad of urticaria, biliary colic and jaundice may result from a ruptured hydatid cyst of the liver or from Ascaris infestation of the biliary tree.

In *urticaria pigmentosa* there are multiple slightly elevated

papules scattered over trunk and extremities. Minor trauma to the lesions releases histamine (and heparin) from the mast cells and produces local urticaria. Occasionally there is systemic involvement with mast cell infiltration of bones and viscera, osteoporosis, hepatosplenomegaly and pancytopenia.

CHOLESTEROL DEPOSITS AND THE LIPIDOSES.—The lipidoses are a group of diseases characterized by abnormal accumulation of lipids in various body tissues (49). The lipid is usually deposited in the form of yellowish waxy lesions, called xanthomas, which are filled with foam cells containing cholesterol and other lipids. By far the most common of these lesions is the *xanthelasma*, a soft yellowish flat or slightly raised lesion appearing on the eyelids, especially near the inner canthi. Xanthelasmas are about ten times as common in hypercholesterolemic subjects as in the general population (1). However, it must be emphasized that about 40% of the patients with xanthelasmas have normal cholesterol levels (21, 50). Extensive lesions are more likely to be associated with a high blood cholesterol level. Xanthelasmas are more common in women than in men, and the incidence is increased in persons with obesity or diabetes mellitus (50). The incidence of coronary heart disease in patients with xanthelasma is roughly 40% (21, 50).

Of greater significance is the *xanthoma tuberosum*, a firm, yellow to brown, raised or pedunculated tumor found especially on the extensor surface of the elbows and knees, in tendon sheaths and on the buttocks. Tendon lesions, occurring mainly in the finger extensors and patellar and Achilles tendons, are referred to as *xanthoma tendinosum*. Small papular xanthomas may occur on the buttocks, the trunk and the palmar surface of the hands. The *xanthoma planum* is a flat lesion found in the creases of palms and soles and on the skin of the neck, chest and back. In all of the foregoing lesions, the lipid material consists mostly of cholesterol.

The *eruptive xanthoma*, or *xanthoma diabeticorum*, is a small, soft yellow nodular lesion surrounded by an erythematous halo and occurring in clusters, especially over the extensor aspects of the extremities and on the buttocks, trunk and palms in patients with hyperlipemia. The lesion consists mostly of neutral fat, although some cholesterol is present.

Finally, in *xanthoma disseminatum*, small brownish yellow papules and plaques are found mainly on the flexor surfaces, especially in the axillae and groin and on the scalp, trunk and

mucous membranes. These lesions occur in patients with the reticuloendothelioses who have normal serum lipids.

The significance of the various lesions is best indicated by a brief classification and discussion of the group of lipidoses, as follows:

(A) *Hypercholesterolemic xanthomatoses.*—(1) *Familial hypercholesterolemic xanthomatosis* is characterized by elevation in blood cholesterol (on a genetic basis), early onset of myocardial infarction and other vascular complications, and the appearance of cutaneous xanthomas. In Piper and Orrild's study (40) of 112 such patients in 12 families, xanthoma tendinosum occurred in 30% of the patients, xanthelasmas in 18%, xanthoma tuberosum and xanthoma planum in 5% and arcus senilis in 24%. In Wheeler's group of 69 such patients, xanthoma tendinosum occurred in 54% (in 91% of those over 40 years old), xanthelasmas in 26%, xanthoma planum and xanthoma tuberosum in 7% and arcus senilis in 6% (53). Subsequent studies have confirmed that xanthoma tendinosum is the most pathognomonic lesion of familial hypercholesterolemic xanthomatosis, although in some series xanthelasmas are more common. Serum lipids may be increased in this disease, but the serum is clear, since there is no elevation of neutral fat. The cholesterol-phospholipid ratio exceeds unity, and most of these patients have elevated S_f 10–40 lipoproteins (21).

(2) *Secondary hypercholesterolemia* may result from biliary cirrhosis. Such patients may exhibit xanthelasmas and xanthoma planum and, rarely, xanthoma tuberosum. The cholesterol-phospholipid ratio is less than 1, the S_f 6–10 lipoproteins are increased, and there is no predisposition to atherosclerosis (21). Similarly, the hypercholesterolemia of hypothyroidism and nephrotic syndrome is probably not associated with excess atherosclerosis, although rarely there are eruptive xanthomas.

(B) *Hyperlipemias.*—(1) In *essential hyperlipemia,* there is no underlying disorder, and there is usually elevation of all blood lipids, including cholesterol and neutral fat, and the serum is milky. Hepatosplenomegaly and episodic abdominal pain are found in about 50% of such patients, as are multiple eruptive xanthomas. The eruptive xanthoma is the characteristic skin lesion, although xanthoma tuberosum has been found in a few patients (1, 34). Xanthelasmas and xanthoma tendinosum are very rare. In contrast with familial hypercholesterolemic xanthomatosis, the prognosis of essential hyperlipemia is usually

good, and vascular complications are probably not excessive unless there is associated diabetes (34, 49).

(2) *Secondary hyperlipemia* may occur in von Gierke's (glycogen storage) disease, chronic pancreatitis, nephrotic syndrome and, most commonly, in uncontrolled diabetes mellitus. Eruptive xanthomas (xanthoma diabeticorum) are not uncommon. In both primary and secondary hyperlipemia, reduction of the hyperlipemia by a low fat diet may bring about the disappearance of the eruptive xanthomas within a few months.

(C) *Normocholesterolemic xanthomatoses,* or *reticuloendothelioses.*—These related diseases are now generally considered to be varying stages of a granulomatous proliferative process, and the presence of cholesterol is regarded as a secondary infiltration. (1) *Letterer-Siwe disease* is a rapidly fatal febrile disease of young children characterized by reticuloendothelial proliferation in multiple organs, including liver and spleen, bones, lymph nodes and lungs. Xanthoma disseminata are the characteristic skin lesions; they often become confluent and petechial, with crusting and scaling which simulates seborrheic dermatitis. (2) *Hand-Schüller-Christian disease* is the more chronic form of reticuloendotheliosis in older children, characterized by the triad of exophthalmos, diabetes insipidus and defects in the skull and other membranous bones. Xanthoma disseminatum occurs in about a third of the patients. (3) *Eosinophilic granuloma* occurs in older children and young adults. There are usually no skin lesions, but occasionally there are erythematous plaques or granulomas.

(D) *Disturbances of phospholipid metabolism.*—(1) *Gaucher's disease* is characterized by abnormal deposits of kerasin in the reticulum cells of the liver, spleen, bones and other tissues of children and adults; anemia and infection are frequent complications. External manifestations include a generalized or patchy increase in the melanin in the skin, especially in exposed areas, and the appearance of brownish pingueculae in the conjunctivas. (2) *Niemann-Pick disease* is marked by abnormal deposits of sphingomyelin in the liver, spleen and central nervous system, with progressive mental deterioration, malnutrition and death in early childhood. The skin is characteristically yellow-brown and wrinkled, and there may be black spots on the mucous membranes. (3) In *Tay-Sachs disease,* there is replacement of brain tissue by an abnormal ganglioside, with progressive blindness and mental deterioration and with death

in infancy or childhood. There are no characteristic external signs, although the cherry-red macular spot is diagnostic.

(E) *Lipoid proteinosis.*—This rare disease is characterized by the appearance of yellowish-white sclerotic plaques and nodules of fatty and proteinaceous material in the skin of the face and mucous membranes, including the tongue, pharynx and larynx, and occasionally the genitalia. The serum phosphatides are usually elevated, and there is a high incidence of diabetes mellitus.

(F) *Angiokeratoma corporis diffusum.*—This disease is discussed on page 24.

ANGIOMAS.—The angiomas, or vascular nevi, are masterfully discussed in Bean's excellent monograph (3). Some of these lesions are important as indicators of internal disease, while others have significance only for cosmetic reasons or in differential diagnosis. In this latter category are the flat nevus flammeus, or port-wine stain; the superficial slightly raised spontaneously involuting strawberry nevus; and the deeper and persistent cavernous hemangioma. The circumscribed slightly raised *cherry angioma,* or De Morgan spot, originally thought to be a stigma of visceral cancer, is now recognized as a normal concomitant of the aging process, occurring in over 90% of persons over 40 and in virtually everyone over the age of 70. Other vascular lesions which appear with advancing age are venous stars, which are irregular stellate dilated cutaneous venules occurring where there has been prolonged increase in venous pressure, particularly in women; venous lakes, which are dark blue venous aneurysms appearing mainly on the ears and face of older men; Fordyce lesions, or small venous angiomas of the scrotum, in older men; and the small varicosities in sublingual veins which Bean has termed "caviar lesions."

Spider angioma.—Of greater significance in internal medicine are the *spider angiomas.* These are arterial telangiectases which consist of a central body or arteriole, sometimes elevated and often pulsatile, and which have branching legs spreading out from the body and a surrounding area of erythema; they characteristically blanch with the application of pressure. They vary in size from 0.2 to 5 or more cm. in diameter (usually 0.5–2 cm.). They occur mainly on the face, neck, upper arms and shoulders, and the thorax; they have very rarely been found even on the lower abdomen and legs. Occasionally they have been seen in mucous membranes, but it is doubtful if they are

ever a significant cause of internal bleeding. Spider angiomas occur mainly in persons with long-standing parenchymal liver disease, especially cirrhosis, but also in prolonged or severe hepatitis. Their appearance and disappearance correlate roughly with deterioration and improvement in hepatic function, although occasionally one spider has been observed to be developing in a patient while another is fading. They are quite uncommon in obstructive jaundice.

Spider angiomas also appear in about two thirds of Caucasian women during pregnancy and disappear rapidly in the postpartum period. The appearance of angiomas during pregnancy is unrelated to prior or subsequent liver disease. The association with pregnancy suggests that estrogens may be an etiologic factor in the genesis of spider angiomas in liver disease as well. It is known that the hepatic detoxification of estrogens is impaired in patients with cirrhosis; and in patients with liver disease, the administration of estrogens has been followed by the development of new angiomas. However, angiomas and palmar erythema have not been produced in patients without liver disease even after the administration of very large doses of estrogen.

Rarely are spider angiomas seen in normal nonpregnant women without any evidence of liver disease. In such cases the angiomas are small in size, few in number and of no apparent significance.

Hereditary hemorrhagic telangiectasia.—The lesions of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) are quite distinct from spider angiomas. They are sharply demarcated mats of coiled vessels without a central arteriole, and they usually do not blanch completely with pressure. Most of the lesions are flat, but occasionally there are hemangiomatous papules. They may occur on any part of the skin or mucous membranes or in the viscera themselves. The skin lesions are especially common on the hands, face, lips and ears and are less often seen in the lower extremities. Rarely the skin lesions may bleed after minor trauma. They are more important as clues to the etiology of internal bleeding, since the mucosal lesions may lead to recurrent severe epistaxis or gastrointestinal hemorrhage. Hematuria and hemorrhage into the brain or meninges are less common. The association with small or large pulmonary arteriovenous fistulas may lead to cyanosis, polycythemia and clubbing, and occasionally to hemoptysis. Telangiectases in the liver have occasionally been described, but probably there is no

increase in the incidence of cirrhosis or portal hypertension.

Blue vascular nevus.—Another external lesion which may be associated with gastrointestinal bleeding is the blue vascular nevus. Bean has reviewed several cases in which bluish nevi were associated with angiomatosis of the gut and enteric bleeding. The skin lesions may be either large cavernous hemangiomas or smaller distensible blue sacs (3).

Generalized telangiectasia.—This is a rare congenital condition which may cause internal bleeding, especially in the gastrointestinal tract. More commonly, generalized telangiectasia occurs with atrophy and mottled pigmentation of the skin (poikiloderma atrophicans vasculare) and is associated with collagen disease, especially scleroderma or dermatomyositis. A similar appearance may be produced in an area of skin which has received extensive radiation.

Sturge-Weber syndrome (encephalotrigeminal angiomatosis). —In this syndrome, port-wine nevi on the face are associated with homolateral meningeal angiomatosis, focal or generalized convulsions, contralateral hemiplegia and mental deficiency. In most cases, there are peculiar intracranial calcifications which follow the convolutions of the cerebral cortex and form characteristic double-line patterns.

Ataxia-telangiectasia.—A familial syndrome of telangiectasia of the bulbar conjunctiva and the butterfly area of the face, cerebellar ataxia and frequent bronchopulmonary infections has recently been described (8). The telangiectasia begins in the conjunctiva in early childhood and slowly extends to involve the face, ears, palate and ultimately the neck and arms. Autopsy studies have shown diffuse cortical cerebellar degeneration and enlarged venules in the cerebellar leptomeninges and white matter.

Von Hippel-Lindau syndrome.—The essential features are hemangiomatous malformations of the retina and central nervous system. Cystic hemangioblastomas of the cerebellum are most common, but occasionally lesions occur in the cervical cord or brain stem. Occasionally there are angiomas of the skin. Angiomas of the liver, pancreatic and renal cysts, and renal carcinoma may be associated. Polycythemia may occur with the cerebellar lesions. There is often a familial incidence.

Angiomas associated with deformity of the extremities.—Two unusual conditions may be considered in this category. In the Klippel-Trenaunay syndrome of hemiangiectatic hypertrophy

of the limbs, an extensive unilateral nevus flammeus or a mass of superficial angiomas is associated with dilatation of deep vessels and distortion and hypertrophy of the involved extremity. In Maffucci's syndrome, dyschondroplasia affecting all the extremities is associated with multiple deep hemangiomas. Patients with Maffucci's syndrome develop extreme and grotesque skeletal deformities and are likely to develop both chondrosarcomas and angiosarcomas.

Angiokeratoma corporis diffusum.—In this rare condition, first described by Fabry, innumerable pinhead-sized discrete raised purplish hyperkeratotic vascular aneurysms are found on the skin, especially on the buttocks, the umbilicus and lower abdomen, and the upper part of the legs. Similar lesions may occur in the retina, joints, myocardium, kidneys, lungs and gastrointestinal tract. Bilateral ankle edema and proteinuria are usually present; hypertension, congestive failure and uremia are common sequelae. Pathologically there are degenerative changes with vacuolation and infiltration with lipoid material in the smooth muscle of many tissues. The most striking involvement is in the smaller and medium-size renal arteries. Large foam cells with clusters of lipoid globules can be found in the urinary sediment and the bone marrow. The few reported cases have thus far been confined to males (22).

SUBCUTANEOUS CALCIFICATION.—A variety of conditions, evident on inspection or palpation, are associated with the precipitation of calcium salts in the skin and subcutaneous tissues. *Dystrophic calcification* may occur at sites of chronic inflammation or trauma even in metabolically normal persons. In *metastatic calcinosis,* amorphous calcium deposits occur characteristically in acid-secreting tissues which are themselves alkaline in reaction, such as kidney, gastric mucosa, lung, and conjunctiva and cornea; also in subcutaneous tissues, especially adjacent to large joints. This condition is seen in the hypercalcemic states such as hypervitaminosis D, milk-alkali syndrome, sarcoidosis and severe hyperparathyroidism, and in chronic renal failure. Paradoxically, metastatic calcification may also occur in the lens of the eye, the basal ganglia and the falx cerebri in hypoparathyroidism and in pseudohypoparathyroidism.

Patients with pseudohypoparathyroidism may also present multiple tiny islands of true bone in subcutaneous tissues, especially in the extremities. Ectopic bone formation also occurs in *progressive myositis ossificans,* in which connective tissue in

skeletal muscles and tendons is gradually transformed into true bone, causing limitation of motion and skeletal deformity.

In *interstitial calcinosis*, calcium salts are precipitated in the presence of normal serum calcium and phosphorus levels and without local infection or trauma. Two variants have been differentiated. In *calcinosis circumscripta*, calcific deposits are localized mainly in the tendons of hands, elbows and knees. In *calcinosis universalis*, the lesions are more extensive and occur also in deeper subcutaneous tissues and within the muscles. Such lesions may ulcerate with extrusion of pastelike amorphous calcific material. Both conditions occur mainly in women; and most such patients have scleroderma, dermatomyositis or a related collagen disease syndrome (52). Recently it has been suggested that the mucopolysaccharide of ground substance may have an abnormal affinity for calcium in these patients.

Hair

The amount and distribution of body hair is often of diagnostic significance. Genetic, hormonal and local factors interact to regulate hair growth. Genetically, both individual and racial factors are important; for example, Orientals and American Indians have less body, facial and axillary hair than most Caucasians, while certain people of Mediterranean ancestry are relatively hirsute. The vast majority of cases of idiopathic hirsutism in women are due to hereditary, rather than to major endocrine, factors, although slightly elevated urinary 17-ketosteroids and a therapeutic effect of cortisone have recently been demonstrated in some of these patients.

The hormonal interrelationships are complex. Androgens increase the growth of the beard and body hair but lead to loss of cephalic hair, particularly in temporal and apical regions. Coarse hair growth on the external ear is a secondary sex characteristic that usually does not appear until after age 25 or 30. For axillary and pubic hair growth, adrenal and testicular androgen (in the male) are most important, but estrogen may also exert a mild stimulating effect. In general, however, estrogen has little effect on the growth of hair. Pituitary growth hormone probably exerts a direct stimulatory effect on hair growth generally. Both growth hormone and androgen act to increase the diameter of individual hairs in the sites affected.

Understanding of these principles facilitates recognition of many of the common endrocrinopathies. For example, loss of axillary and pubic hair is a valuable sign of pituitary deficiency in either sex or of adrenal insufficiency in the female. The hypogonadal male, lacking in androgen, characteristically has not only deficiency of body and beard hair but also a superabundance of cephalic hair; his axillary and pubic hair is deficient but usually not wholly lacking. Similarly, the increased estrogen-androgen ratio in the cirrhotic patient leads to loss of body hair, and usually also to loss of axillary and pubic hair. Body hair is strikingly deficient in patients with hemochromatosis, presumably because of the combination of hepatic and testicular damage.

In evaluating suspected abnormal hair patterns, the normal changes of aging must be kept in mind. There is a progressive loss of axillary, pubic and general body hair, especially on the legs, in elderly persons. Most or all of the axillary hair is lost in about one fourth of persons over 60 years of age (more often in women), but complete loss of pubic hair is very rare. Thus the loss of pubic hair in elderly persons is of much greater diagnostic significance than is axillary alopecia (36).

In Cushing's syndrome or with adrenocorticoid therapy, an increase in lanugo-like general body hair is sometimes found. The scalp hair becomes lusterless and unable to hold a wave.

Precocious development of pubic and axillary hair in either sex may result from virilizing tumors or hyperplasia of the adrenal cortex or the gonads. When such lesions occur in the mature female who already has axillary and pubic hair, the appearance of facial hirsutism is the major change in hair distribution; balding is less common but is a more specific sign of virilism. A relative preponderance of androgenic substances is probably also responsible for increased hair growth on the upper lip and on the chin in the postmenopausal woman. The mechanism of hirsutism in the Stein-Leventhal syndrome (with amenorrhea and polycystic ovaries) is unknown, although an adrenal cortical etiology has been suggested. The hirsutism is not accompanied by balding or other evidence of virilism.

In adult hypothyroidism, there is a loss of axillary and pubic hair as well as the classic loss of lateral eyebrow hair. The former change may well be due to decreased adrenocortical function in these patients. Residual hairs are usually dry and coarse and tend to grow out at right angles to the body surface.

On the other hand, hypothyroid children may show an increased growth of fine lanugo-like hair on the trunk and arms. In thyrotoxicosis, the hair is typically fine and silky, and there may be some loss of hair from the scalp and the axillae. In acromegaly, the individual hairs are coarse and thick, but true hirsutism is uncommon.

Brain damage, whether due to trauma, encephalitis or congenital defects, may be associated with excessive growth of body hair. Increased hair growth also occurs in immobilized limbs, as in polyneuritis or in limbs under plastic casts. Porphyria, especially the congenital (erythropoietic) variety, is another poorly understood cause of hirsutism.

Alopecia is usually only of local significance, but occasionally systemic factors are involved. Hereditary alopecia (common baldness) of normal males requires three factors for its production: genetic susceptibility, adequate circulating androgen and the attainment of a critical age. Congenital alopecia may be an isolated abnormality but is usually associated with other ectodermal defects. Severe febrile illnesses, such as typhoid fever or influenza, may be followed by a symptomatic alopecia which is usually transient. Certain chemicals and drugs, such as thallium, as well as many of the agents used in cancer chemotherapy, are all capable of inducing extensive hair loss, which usually occurs 2 or 3 weeks after the toxic insult. A patchy "moth-eaten" alopecia areata may be due to secondary syphilis. Permanent cicatrizing alopecia areata may be due to lupus erythematosus, to deep pyogenic or fungal infections or to radiation. Both hypothyroidism and thyrotoxicosis may cause moderate loss of hair from the scalp. Alopecia areata may occur in hypoparathyroidism. Early onset of frontal alopecia is seen in patients (of either sex) with dystrophic myotonia. Nevertheless, in the vast majority of cases of alopecia areata, as well as in the more extensive alopecia totalis and universalis, there is no evidence of endocrine or other systemic disorder.

Gray hair is usually a normal accompaniment of the aging process, of variable time of onset. Premature graying is often a familial trait of no particular significance. However, there is a high incidence of pernicious anemia in such patients. Graying may also be a sequel of acute febrile states, debilitating systemic disease or severe emotional stress. Localized patches of grayness may occur in vitiligo, during regrowth of alopecia areata, following peripheral nerve injury, or rarely in the Vogt-Koyanagi

syndrome, which includes vitiligo, alopecia, bilateral uveitis and deafness.

Lightening of hair color to a reddish appearance is common in the malnutrition of kwashiorkor, and has been reported in a patient with severe ulcerative colitis.

Facies

Many diagnoses can be made, or strongly suspected, by simple observation of the face. Anxiety and depression, pain or pleasure, schizophrenic withdrawal, manic agitation and other emotional states are all mirrored in the facial expression. The vacant countenance of the idiot is often characteristic. In scleroderma, the facial skin is often smooth and tightly drawn, resulting in rigidity of expression. More common is the "mask facies" of Parkinsonism, which is associated also with tremor and hypersalivation.

Other neurologic disorders may be recognized by the appearance of the face. Residual facial weakness is common in patients with cerebrovascular disease. The drooping eyelids and lax jaw of the severe myasthenic are characteristic. The waxy yellowish-red papules of adenoma sebaceum are seen in the "butterfly area" of the face in patients with tuberous sclerosis. Angiomas on the face may be indicative of similar lesions in the brain.

The dry roughened skin, sunken eyes, hollow cheeks and prominent bony structure of the Hippocratic facies have been recognized for generations. The findings are those of dehydration and cachexia, such as may occur in prolonged and severe infections or in terminal malignancy.

Both vascular disturbances and disorders of pigmentation are likely to be particularly striking in the face. Generalized dilatation of superficial vessels is the hallmark of the chronic alcoholic; when this is combined with spider angiomas and a trace of jaundice, Laennec's cirrhosis can be strongly suspected. The "butterfly rash" of lupus erythematosus is well known. The plethoric facies of polycythemia is due to the combination of cutaneous vasodilatation and an elevated hematocrit. A malar flush may occur in patients with fever or mitral stenosis.

Many of the *endocrinopathies* have characteristic facial appearances. In acromegaly, enlargement of facial bones is especially marked in the mandible and maxilla; the lower jaw, lips,

nose, tongue and ears are all very prominent, and the teeth may be widely separated. Cushing's syndrome is marked by hirsutism and a plethoric moon face.

In hyperthyroidism, exophthalmos and other eye signs, a bright staring, often startled, expression, and emotional lability result in an unmistakable picture. On the other hand, a dull listless expression, with coarse features and a large tongue, a dry scaly skin, periorbital edema and sparse hair, especially in the lateral third of the eyebrows, are a diagnostic combination in myxedema. (Facial pallor and periorbital edema with bags under the eyes may also be seen in patients with chronic renal disease.) Similarly, in children with cretinism, mental retardation is associated with periorbital edema, dry coarse skin and hair, and a large thick protruding tongue. This picture must be distinguished from that of mongolism, in which protrusion of the tongue is due to the smallness of the oral cavity. Mongoloids have a general decrease in skull size with a small orbit and an underdeveloped nose, associated with slanting eyes, medial epicanthus and frequently other congenital anomalies.

A saddle-nose deformity is one of the stigmata of congenital syphilis, but it may also result from the osteitis of acquired syphilis. Perforation of the cartilaginous septum may be due to trauma, to infection, to Wegener's granulomatosis or to inhalation of chromic acid fumes. Perforation of the bony septum is usually due to syphilis.

Severe idiopathic infantile hypercalcemia may be recognized by the characteristic "elfin facies" with prominent epicanthic folds and underdevelopment of the bridge of the nose and the mandible (44).

A coarse thickened "leonine facies" due to cutaneous hypertrophy is classically seen in lepromatous leprosy; but it also occurs in some patients with mycosis fungoides and in the pachydermoperiostitis that may accompany clubbing of the fingers.

In Paget's disease, there is likely to be a massive and asymmetrical enlargement of the calvarium, with prominence of the temporal vessels on the affected side. In gargoylism, or Hurler's syndrome, the peculiar coarsening of features with gross thickening of the eyebrows, nose and lips, sometimes associated with corneal opacity and with mouth breathing due to deformity of the skull, may be the facial clue to an abnormality of polysaccharide metabolism resulting in damage to many organs (35).

ORBIT AND LIDS.—The eyelids, because of the low tissue pressure, are a favored site for localization of edema. Edema of the lids is especially characteristic of acute nephritis and the nephrotic syndrome. In trichinosis, eyelid edema is secondary to inflammatory involvement of the extraocular muscles; chemosis and conjunctival injection are usually present also. Xanthelasmas (see discussion on page 18), while occurring in many normal persons, are more common in patients with coronary artery disease. Exophthalmos, lid lag, retraction of upper lids, limitation of convergence and diminished frequency of blinking are all characteristic of Graves' disease. Less commonly, exophthalmos may be due to leukemia or other neoplasms or to local pathology. Unilateral exophthalmos is suggestive of a local cause but is seen occasionally in hyperthyroidism. Ptosis, enophthalmos, miosis and facial anhidrosis comprise Horner's syndrome, which results from interruption of cervical or upper thoracic pathways, as by a bronchiogenic carcinoma.

SCLERA.—Mild degrees of icterus are often best appreciated in the sclerae. The blue sclerae of osteogenesis imperfecta are due to the thinness of the sclerae, which allows the choroid pigment to show through (35). In ochronosis, patches of light brown or bluish gray pigmentation may be found in the sclerae on either side of the corneal limbus. Pingueculae are yellowish white wedge-shaped thickenings of subconjunctival fibrous tissue in the interpalpebral zone on either side of the cornea. They usually appear first on the nasal side, and they are very common in normal elderly persons. However, large yellowish brown pingueculae are characteristic of Gaucher's disease (49). Episcleritis and episcleral nodules, usually occurring on the temporal side of the cornea, are most often a manifestation of rheumatoid arthritis.

CONJUNCTIVA.—Pallor of the palpebral conjunctivae is one of the more dependable signs of anemia. Acute conjunctivitis is characteristic of Reiter's syndrome, leptospirosis and many viral infections. Stimson's line is a sharply demarcated line of intense congestion along the outer margin of the lower lid which appears early in the course of measles, about 24 hours before the Koplik spots. The line is soon obscured by a general conjunctivitis.

Exudative erythema multiforme may involve the conjunctiva as well as the uveal tract and anterior chamber. *Keratoconjunc-*

tivitis sicca refers to a dryness and chronic inflammation of the cornea and conjunctiva which results from the absence of tears in patients with chronic lacrimal gland disease. When this is associated with parotid enlargement and arthritis, *Sjögren's syndrome* is said to be present (38).

In vitamin A deficiency, xerophthalmia is followed by keratinization of the cornea and the appearance of Bitot's spots, superficial grayish white foamlike spots, usually starting near the temporal limbus. In hypercalcemia, calcium deposits may appear as small crystal-clear glasslike particles in the bulbar conjunctiva on either side of the cornea, or in the tarsal conjunctiva of the everted upper lid. However, slit-lamp observation is often required (13).

CORNEA.—The familiar *arcus senilis* is an opaque grayish white ring of lipid material in the periphery of the cornea (12). Usually there is a clear zone between the arcus and the limbus. Arcus senilis usually begins and is most prominent in the upper and lower quadrants of the cornea. It is more common in Negroes than in Caucasians. The lesion develops at an earlier age (in the forties) in males than in females, and there is a rapid increase in incidence after age 50. Boas (7) found a somewhat higher incidence of coronary artery disease in middle-aged persons with arcus than in those without arcus. However, at all ages, there are some persons with arcus in whom no evidence of coronary artery disease or hypercholesterolemia can be found. Furthermore, in unselected native populations, identical cholesterol values have been found in patients with and without arcus senilis (26). It appears that, although the appearance of arcus in young persons (under 40) may be associated with hypercholesterolemia and an increased incidence of coronary artery disease, the correlation in older persons is very poor.

Band keratopathy is a frequent finding in patients with prolonged hypercalcemia. Gray, granular deposits of calcium form an opaque rim in the superficial stroma of the cornea just beneath the epithelium but leave a clear zone adjacent to the limbus. The deposits are denser at the periphery and gradually fade off centrally. Characteristically, the lesion is most prominent at the medial and lateral margins of the cornea, in contrast with arcus senilis, which is most prominent superiorly and inferiorly. In contrast to the more common band keratitis which may follow intraocular inflammation, there are usually clear areas within the zone of opacity in the keratopathy of hyper-

calcemia. Good illumination and sometimes a slit lamp are required to demonstrate the lesion (13).

The pathognomonic *Kayser-Fleischer ring* of Wilson's disease consists of greenish brown copper deposits in Descemet's membrane on the undersurface of the corneal limbus. In cystinosis, slit-lamp examination may demonstrate myriads of refractory needle-shaped particles scattered throughout the cornea; but to the unaided eye, only a faint haziness can sometimes be noted.

A deep interstitial keratitis is one of the stigmata of congenital lues. Similar lesions may cause blindness in lepromatous leprosy and tuberculosis. Corneal clouding due to opacities in the deeper layers of the cornea also occurs in most patients with gargoylism (35).

Uveitis.—While many affections of the uveal tract require ophthalmoscopic or slit-lamp examination for detection, some can be observed by simple inspection, particularly when the iris and ciliary body are involved. Anterior uveitis may result in circumcorneal injection of the anterior ciliary vessels; in entry of leukocytes into the anterior chamber, causing clouding or opacity or keratic precipitates; or in granulomatous nodules, formation of synechiae or other inflammatory changes of the iris itself. The systemic causes of anterior uveitis include: tuberculosis, sarcoidosis, syphilis, brucellosis, histoplasmosis, toxoplasmosis, rheumatoid arthritis and spondylitis, ulcerative colitis and, rarely, leptospirosis. Sarcoidosis and toxoplasmosis are probably the most common systemic causes of granulomatous uveitis in adults, although toxoplasmosis causes chiefly a posterior uveitis or chorioretinitis. Rheumatoid arthritis may be the chief offender in children.

Behçet's disease is a form of exudative erythema multiforme in which hypopyon is a prominent feature. In the Vogt-Koyanagi syndrome, bilateral uveitis is associated with vitiligo, deafness, and patchy alopecia and graying of hair.

The old theory that foci of infection elsewhere in the body may cause nongranulomatous uveitis is now seriously questioned. However, the data of Woods (56) indicate that a high percentage of such patients give positive skin reactions to streptococcal vaccines.

Brushfield spots are white or light yellow speckles due to aggregations of pigment arranged in a circle in the outer half of the iris. They occur chiefly in mongoloid patients with blue irises, and are among the most consistent stigmata of mon-

golism. However, a speckled iris is occasionally seen in normal blue-eyed persons.

PUPILS.—Examination of the pupils and the extraocular muscles is of critical importance, chiefly in the diagnosis of neurologic disease. An isolated ocular palsy may be an early manifestation of diabetes. The Argyll-Robertson pupil is a familiar sign of neurosyphilis, occurring in about 50% of cases. It is not absolutely diagnostic, however, since it is seen rarely in multiple sclerosis and transiently in Wernicke's encephalopathy.

LENS.—Lenticular opacities, or cataracts, have been associated with a number of systemic disorders (37). In some cases the cataracts are large enough to be apparent to the unaided eye.

Congenital cataracts may be found in infants born to mothers who had German measles in the first trimester of pregnancy. Such children have a high incidence of associated congenital heart disease, deaf-mutism and other defects.

There is a high incidence of acquired cataract developing at an early age in mongoloids and in children with other congenital anomalies. In Werner's syndrome, cataracts developing in early adulthood are associated with short stature, slender extremities, premature aging, skin changes resembling scleroderma, and sometimes hypogonadism and diabetes mellitus. In the related but less common Rothmund's syndrome, cataracts appear in early childhood and are associated with telangiectasia and pigmentary changes in the skin. In myotonic dystrophy, cataracts in the adult are associated with myotonia, muscular atrophy, and usually hypogonadism and frontal alopecia.

In diabetes mellitus, there is a slightly increased incidence of senile cataract. More important is the rapidly forming bilateral cortical cataract which may occur in poorly controlled juvenile diabetics. Similar cataracts occur in infants with galactosemia; these may disappear if milk is removed from the infant's diet before the age of 3 months.

Hypocalcemia may give rise to the formation of posterior lamellar or subcapsular cataracts and must always be considered when cataracts are found in young people. The most common cause is hypoparathyroidism, but similar lesions have been seen in pseudohypoparathyroidism and in severe osteomalacia or rickets.

There is also a high incidence of early cataract formation in patients with atopic dermatitis. In the aortic arch syndromes ("pulseless disease" due to obliterative endarteritis or thrombo-

sis at the root of the great arterial trunks), visual symptoms are common; the ocular findings include cataracts, iris atrophy and corneal opacities.

Subluxation of the lens (ectopia lentis) is a major feature of Marfan's syndrome, which was discussed on page 7.

Ears

Close examination of the external ears occasionally provides a clue to the diagnosis of systemic disease. Gouty tophi, familiar as nontender yellow-white swellings representing urate deposits, are found especially in the helix or anthelix of the ears. They must be distinguished from the normal Darwinian tubercle which occasionally projects from the posterior portion of the helix. Bluish-black pigmentation of the aural (and nasal) cartilages, rendering them opaque to transillumination, may occur in ochronosis as a result of deposition of a polymer of homogentisic acid. Hard inflexible ears resulting from calcification of auricular cartilage may occur in Addison's disease and rarely in acromegaly, ochronosis and pseudo-hypoparathyroidism (47); they may also be secondary to trauma or frostbite. Long ears are said to be common in patients with pernicious anemia. Gross malformation of the ears is often associated with other congenital anomalies, especially of the urinary tract; bifid ureters and unilateral or bilateral renal agenesis are the most common associated defects (27). In mongolism, the ears are small and simply convoluted, and frequently no lobule is present.

Parotid Gland

The acute parotitis of mumps may be the clue to the diagnosis of obscure abdominal pain due to mumps pancreatitis or oophoritis.

Chronic parotid enlargement may occur in alcoholic patients with cirrhosis (42), in malnutrition from other causes and occasionally in older persons without other evidence of malnutrition. *Mikulicz's disease* refers to the painless enlargement of the salivary glands, with lymphocytic infiltration of the glandular parenchyma and intraductal proliferation of epithelial and myoepithelial cells. It usually occurs in middle-aged women and is often associated with keratoconjunctivitis sicca, rheuma-

toid arthritis and other systemic manifestations (Sjögren's syndrome) (38). *Mikulicz's syndrome* is parotid enlargement resulting from lymphoid hyperplasia within the gland, such as may occur in leukemia, lymphoma, tuberculosis, sarcoidosis and possibly in lupus erythematosus.

Parotid enlargement must not be confused with benign hypertrophy of the masseter muscles, which may result from habitual chewing or clenching of teeth.

Oral Cavity

Stomatitis is usually secondary to local factors, such as poor hygiene; occasionally it is related to systemic disease as in uremia, acute leukemia or mercury poisoning. Recurrent aphthous stomatitis is a self-limited disease which bears no apparent etiologic relationship to systemic disease or to herpetic or other known viral infection. The oculomucocutaneous syndromes are discussed on page 10.

In many of the acute *viral infections*, the rash appears as an enanthem on the buccal mucosa and soft palate, as well as on other mucous membranes and on the skin. Most of these lesions are nonspecific. However, Koplik spots are tiny bluish white lesions, usually surrounded by a zone of erythema, which appear opposite the first molars and are quite diagnostic of early measles. Tiny grayish white vesicles or ulcers on the soft palate, tonsils or anterior pillars are characteristic of herpangina due to Coxsackie A virus infection. Petechiae on the soft palate are suggestive of infectious mononucleosis, but they occur in other conditions as well.

Pigmentation of the buccal and gingival mucosa may occur in any generalized melanosis. The pigmentation may be either diffuse or spotty. It is most often seen in hemochromatosis, Addison's disease, the intestinal polyposis syndrome and in normal Negroes (28).

Gingival hyperplasia is an occasional reaction to therapy with diphenylhydantoin sodium. In the absence of drug treatment, hyperplasia of the gums is suggestive of acute monocytic leukemia, especially when accompanied by hemorrhage and ulcerative stomatitis. Bleeding gums may occur also in scurvy and in any severe thrombocytopenia. A blue-black lead line in the gums adjacent to the gingivodental margin is usually due to the deposition of lead sulfide; however, the lesion is not absolutely

diagnostic, since similar lines may be produced by bismuth, mercury and other heavy metals. Gingivitis and periodontitis are especially common in diabetic patients and may interfere with control of the diabetes.

The notched, peg-shaped, tapered Hutchinson's teeth of congenital syphilis are still seen occasionally. Greenish pigmentation of the deciduous teeth of children may be the sequela of neonatal jaundice. Red or reddish brown teeth are pathognomonic of congenital porphyria. An epulis, or giant cell tumor of the jaw, may be a clue to the diagnosis of hyperparathyroidism. A high arched palate is characteristic of Marfan's syndrome.

Halitosis is usually due to oral or pharyngeal infection or to poor local hygiene rather than to systemic disease. Sinusitis and chronic bronchopulmonary disease may also be responsible for a foul breath. The odor of alcohol on the breath is quite distinctive. Other breath odors of diagnostic significance include the sweet acetone odor of ketosis and the ammoniacal or uremic breath of severe nitrogen retention. The pungent mousy *fetor hepaticus* of severe liver disease has been attributed to the presence of methylmercaptan and related compounds in the breath.

TONGUE.—Examination of the tongue has a long and venerable tradition in clinical medicine. The furrowed *scrotal tongue* is a normal variant, and the migratory, changing superficial patterns of the partially denuded *geographic tongue* are also without diagnostic significance. A *dry tongue* may result from mouth breathing, salivary gland disease or dehydration. *Coated tongue* results from the accumulation of bacteria, food particles and chiefly desquamated keratin from the filiform papillae, and may be found with fever, dehydration, heavy smoking, chronic debilitating disease or any situation in which there is impairment in the normal cleansing function of the mouth.

Burning or *sore tongue* may be due to the atrophic glossitis of iron deficiency or macrocytic anemia, but most frequently it is of psychogenic origin. *Atrophic glossitis* with loss of filiform papillae may result from severe iron deficiency, pernicious anemia or deficiency of B vitamins resulting from malnutrition or malabsorption. A beefy, swollen, smooth, red tongue is characteristic of niacin deficiency; cheilosis and stomatitis are often associated. The deeper colored magenta tongue suggests riboflavin deficiency. Glossitis may also be due to therapy with folic acid antagonists.

Black hairy tongue is due to hyperkeratinization and over-

growth of filiform papillae; it is usually secondary to the alterations in bacterial flora induced by antibiotic therapy. Monilial infection may be associated. However, the typical oral manifestation of *moniliasis* is a white curdy or flaky plaque which may be on buccal, palatal and lingual orpharyngeal mucosa; mycelial forms can be demonstrated microscopically. Oral moniliasis usually occurs in patients with chronic debilitating disease or after prolonged antibiotic therapy; it may also be seen in normal newborns.

Syphilis of the tongue is rarely seen nowdays, but the diagnosis must always be considered in a patient with leukoplakia involving tongue or buccal mucosa or in any unexplained glossitis. Primary chancres are occasionally seen on the lips and tongue; the highly infectious ulcerated "mucous patches" on the buccal mucosa, palate or tongue are the oral equivalent of the maculopapular rash of secondary syphilis. Gummas may also occur in the tongue or palate.

Macroglossia is a characteristic of certain conditions. Slight enlargement of the tongue may be seen in pellagra and other deficiency states, polycythemia, scrotal tongue, sublingual mumps and in local inflammatory processes. More significant macroglossia occurs in primary amyloidosis, acromegaly, hypothyroidism and in infants with glycogen storage disease. A transient macroglossia may result from angioneurotic edema or from bleeding into the substance of the tongue in patients with coagulation defects (e.g., hemophilia).

Hands

The hands provide many clues for the diagnosis of internal disease (45). Cold sweating hands may be found in Raynaud's disease, in neurocirculatory asthenia and in some patients with rheumatoid arthritis; however, if there is active rheumatoid disease in the hands, they are likely to be warm and moist. Warm, moist and tremulous hands are the typical findings of thyrotoxicosis. Enlargement of the hands due to overgrowth of bone occurs in acromegaly. Enlarged hands may occur in myxedema as a result of soft-tissue swelling.

The *mongoloid hand* is short and relatively broad with stubby fingers, a widely set thumb, a short incurved fifth finger and only a single transverse palmar crease. Dermatoglyphic study shows extreme transversality of ridges in the distal portion of

the palm and frequently the occurrence of a "triradius" in the central area of the palm. A broad, stubby-fingered claw hand with flexion deformities is characteristic of Hurler's syndrome (35).

Syndactylism and polydactylism are frequently associated with other congenital anomalies. Some cases of polydactylism are associated with mental deficiency, obesity and hypogonadism, comprising the Laurence-Moon-Biedl syndrome.

Long spidery fingers, or *arachnodactyly,* is the hallmark of Marfan's syndrome. Long loose-jointed extremities, ectopia lentis and weakness of the aortic media, which predisposes to aortic regurgitation or dissecting aneurysm, are the major additional defects. Atrial septal defects or cystic disease of the lung may also be associated (35).

The *arthritides* can frequently be differentiated by examination of the hands. Thus, rheumatoid arthritis is typically marked by symmetrical fusiform swelling of proximal interphalangeal joints, with ulnar deviation and other deformity in advanced cases; degenerative joint disease by Heberden's nodes and involvement of distal interphalangeal joints; and gout by asymmetrical involvement with tophi around the joints or tendons.

The *palms* are often a good place to look for evidence of anemia; disappearance of the red color of the creases of the hyperextended palm usually indicates a hemoglobin concentration of less than 7 Gm./100 ml. Palmar erythema is a common finding in liver disease, in rheumatoid arthritis and less often in pregnant women. Dupuytren's contracture is frequently seen in chronic alcoholism with cirrhosis (55).

The *capillary pulse* is a classic sign of aortic regurgitation; but it may also be seen in other conditions with increased pulse pressure, as in patent ductus arteriosus and arteriovenous fistula, or as a result of cutaneous vasodilatation, as in fever and thyrotoxicosis.

Clubbing of the fingers is characterized by thickening of connective tissue, especially at the base of the nail bed, causing curving of the nail plate with an increase of the obtuse angle between the nail and the skin at its base to 180° or more. Typically, the nails are "floating" or freely movable on pressure. Simple convex "beaking" is of no diagnostic significance. Both beaking and clubbing may be familial traits, especially in Ne-

groes. The most advanced changes, with bulbous deformity of the fingertips, are seen in patients with cyanotic congenital heart disease. Clubbing also occurs in chronic lung disease, especially bronchiectasis, lung abscess, bronchiogenic carcinoma and arteriovenous fistulas; in chronic infections, especially subacute bacterial endocarditis; and occasionally in biliary cirrhosis, regional enteritis or ulcerative colitis. Unilateral clubbing may occur with a superior sulcus tumor, an aortic or subclavian artery aneurysm or chronic dislocation of the shoulder.

The xanthomas and the manifestations in the hands of the endocrinopathies, collagen disease and bacterial endocarditis are discussed elsewhere.

Nails

In addition to clubbing, abnormalities of the nails, particularly the fingernails, may provide other clues to the presence of internal disease. Many of the anomalies of nail shape or growth are on a congenital basis and of no particular significance. However, *Beau's lines* are transverse furrows in the nails, usually resulting from arrest of growth at the time of a major illness, such as a myocardial infarction or febrile infectious disease. The illness may be dated by the knowledge that normal nail grows out at the rate of about 0.1 mm./day and that it takes the nail about a month to emerge from the proximal nail fold. Longitudinal furrows or fissures are due to irregularities in the matrix, which may be of congenital or traumatic origin or a consequence of the aging process. In *koilonychia* or spoon nail, the nail becomes thin and concave; this is most suggestive of hypochromic anemia, but is also seen occasionally in polycythemia, thyroid dysfunction and malnutrition. In *onycholysis*, there is separation of the nail from the distal portion of the nailbed, resulting in irregularity of the free margin; this is most suggestive of thyrotoxicosis (Plummer's sign), but similar changes may occur as a result of trauma, chemical irritants or hypothyroidism. Both koilonychia and onycholysis were formerly seen in patients with secondary syphilis.

True *leukonychia*, or whiteness of the nail, results from air entrapped between the epithelial cells of the developing nail. It is usually seen in the form of transverse white bands (*Mee's lines*), which are very common in normal persons, especially if

the nail bed has been traumatized, as in a manicure; however, rarely these striae may result from arsenic or thallium intoxication or from psoriasis. *Apparent whiteness* of the nails is common in patients with cirrhosis (48). The nail itself is normal, but the underlying matrix is less than normally adherent to the underlying vascular tissue, thus resembling the normal lunule; usually there is a distal pink zone of normal nail bed. Paired transverse white bands have recently been described as a sign of chronic hypoalbuminemia, regardless of cause (39).

Colored nails are seen occasionally. Argyria causes a slate blue discoloration of the nail bed, which begins just distal to the lunule. Blue lunules have been observed in patients with Wilson's disease. Psoriasis, eczema or onychomycosis may color the nails yellow or brown. Green nails have resulted from Aspergillus and Pseudomonas infections. With subungual hemorrhage, the nail appears blue or black. A variety of chemical agents may cause pigmentation of the nails. Longitudinal bands of melanotic pigment are very common in the nails of Negroes; when seen in Caucasians, they may be due to pigmented nevi in the nail matrix.

Psoriasis of the nails is manifested by multiple punctate depressions or pits, with thickening and discoloration of the nail and accumulation of subungual debris. Such lesions may be associated with rheumatoid arthritis, particularly the psoriatic variety with involvement of distal interphalangeal joints. *Monilial infections* are characterized primarily by chronic paronychial disease and are not true onychomycoses. Chronic moniliasis and dystrophic lesions of the nails and skin are frequent findings in patients with idiopathic hypoparathyroidism and adrenal insufficiency, particularly in children. Monilial infections are also common in diabetics.

A variety of ectodermal dysplastic conditions may cause atrophy of the nails. In hereditary arthrodysplasia, absent or rudimentary nails are associated with absence or lateral displacement of the patellas. A syndrome of atrophy of the nails, alopecia, diffuse skin pigmentation and intestinal polyposis has also been described (15).

Splinter hemorrhages under the nails are seen in subacute bacterial endocarditis, trichinosis, occasionally in mitral stenosis without infection and rarely in normal persons. In occlusive arterial disease, nails are likely to become thickened and rough; in vasospastic conditions, pterygium, or overgrowth of cuticle at

the base of the nail, is more common. Finally, *nail biting* is, of course, a neurotic trait, which may be attributable to habit, tension or insecurity.

Lower Extremities

Edema of the legs and feet is, of course, a familiar manifestation of vasculitis, hypoalbuminemia, or cardiac, renal or hepatic disease. The signs of thrombophlebitis in the legs may be a clue to the diagnosis of pulmonary embolism. Calf tenderness is common in nutritional polyneuropathy. Necrobiosis lipoidica diabeticorum and erythema nodosum have a predilection for the shins, nodular vasculitis and erythema induratum for the calves, and nodular panniculitis for the thighs.

Ulcerations on the lower extremities are most commonly a consequence of arteriosclerosis, varicose veins, trauma or local infection. Systemic causes include the chronic hemolytic anemias, most commonly sickle cell disease but also hereditary spherocytosis and thalassemia; periarteritis nodosa and rheumatoid arthritis, especially when the latter is associated with Felty's syndrome; polycythemia; cryoglobulinemia; erythema induratum; and the pyoderma gangrenosum of ulcerative colitis.

Pigmentation of the lower legs usually results from the combination of extravasation with hemosiderin deposition and secondary melanization. This condition is most common in patients with varicose veins, but it also occurs in hemochromatosis, the chronic purpuras, the hemolytic anemias and in Gaucher's disease.

Examination of the feet is frequently helpful in the differential diagnosis of *arthritis*. The feet are frequent sites of tophus formation; and acute podagra, involving the metatarsophalangeal joint of the great toe, is the most common initial manifestation of gout. Bilateral and symmetrical hammer toes, depression of metatarsal heads and hallux valgus are common features of rheumatoid arthritis.

Keratodermia of soles and palms is particularly common at the menopause. *Keratoderma blenorrhagica*, the heaped up, yellow-brown, crusted horny plaques on palms and soles and on the dorsa of hands and feet, was originally described in gonorrhea but is now most often seen with Reiter's syndrome.

Endocrine Disorders

The endocrinopathies include some of the diseases most likely to be diagnosed or suspected from their external manifestations. Obviously, not all of these signs will be found in every patient with the disease concerned.

Diabetes.—In *diabetes mellitus*, any of a variety of skin lesions may appear. Dryness of the skin may result from dehydration and asteatosis. Recurrent furuncles and other pyogenic infections are common. Pruritus, especially pruritus valvae due to moniliasis, may be the first sign of the disease; monilial infections may occur in other sites as well. Ischemic ulcers, cold hairless toes and gangrene may result from arteriosclerosis obliterans. Hyperlipemic patients may have showers of eruptive xanthomas, especially on the extensor surface of the extremities.

Necrobiosis lipoidica diabeticorum refers to the soft, slightly depressed, brownish plaques of necrosis and atrophy, often infiltrated by cholesterol-laden histiocytes and covered by thin shiny skin, found mainly over the shins. Ninety per cent of the cases occur in women. The lesions are usually seen in severe diabetics of long standing; but occasionally they may be an early sign, and they may occur in the absence of diabetes. They are quite unlike the lesions of insulin lipodystrophy, which may be either atrophy and depression or fibrosis and thickening of the subcutaneous tissue at the site of insulin injections.

Thyroid disorders.—Exophthalmos, tremor and warm moist sweaty skin are a familiar triad in the patient with Graves' disease. Plummer's sign, discussed previously, may also suggest a diagnosis of thyrotoxicosis. Redness of the elbows is frequently present. Localized pretibial myxedema may appear as elevated hard yellow-brown plaques or nodules on the shins, especially in the patient with treated hyperthyroidism. Both vitiligo and increased melanin pigmentation are occasionally seen in hyperthyroid patients.

The hypothyroid patient typically has a cool, very dry and coarse skin, with nonpitting edema in the subcutaneous tissue of trunk and extremities and with sparse coarse hair; alopecia of the lateral eyebrows is characteristic of hypothyroid adults. Dystrophic changes in the nails are common. The yellow hue

of the skin is due to a combination of carotenemia, anemia and myxedema.

ADRENAL DISORDERS.—The stigmas of Cushing's syndrome include truncal obesity, a round plethoric facies, acne, hirsutism, buffalo hump and a thin fragile skin with striae and easy bruising. Recently this syndrome has been described in association with oat cell carcinoma of the lung and a peculiar secondary adrenocortical hyperplasia (32).

In *Addison's disease,* pigmentation may assume any of several patterns: (1) diffuse melanization of the skin, even where unexposed; (2) pigmentation of the oral mucosa; (3) hyperpigmentation of pressure areas, body folds and prior existing scars; (4) multiple dark freckles, particularly over the upper body area; (5) deepening of hair color; and (6) vitiligo (24). The mechanism for increased melanin pigmentation appears to be an increased release of pituitary melanocyte-stimulating hormone resulting from decreased adrenocortical function (33). Patients with Addison's disease also show axillary and pubic hair loss, especially in women. They are slender and often have hard inflexible ears and small weak voices.

PARATHYROID DISORDERS.—In hyperparathyroidism, there are usually no external manifestations. However, band keratopathy is sometimes found; occasionally there are subcutaneous calcifications; and rarely an epulis, or giant cell tumor of the jaw. Long-standing hypoparathyroidism generally results in a dry scaly skin, scanty hair and dystrophic changes in the nails. The nail changes are often associated with moniliasis, especially in children (14). Patients with hormone-resistant pseudohypoparathyroidism have a distinctive appearance, marked by a round broad face, a short thickset body, short metacarpal bones, a relatively dull sensorium and subcutaneous foci of ossification. The short metacarpals in these patients can usually be demonstrated by the absence of one or more knuckles in the closed fist (Albright's sign).

GONADAL DISORDERS.—The signs of gonadal dysfunction vary not only with the nature of the endocrine pathology but also with the age of onset of the disturbance. In general, the earlier the onset, the more severe are the manifestations. Thus, when *male hypogonadism* is present before puberty, the testes, penis and other accessory sex organs are hypoplastic; the general body contours are feminine, with broad hips and a tendency toward gynecomastia; the delayed closure of the epiphyses makes for tall stature; the skin is fine, pale and yellowish; and there is a

deficiency of pubic, axillary and facial hair, with an abundance of hair on the scalp. Obviously, an accurate diagnosis cannot be made until after the expected time of puberty. When male hypogonadism appears after puberty, the external genitalia and body contours are already determined and all changes are less marked. The testes change little in size but lose their normally firm consistency.

Patients with gonadal dysgenesis have infantile sexual organs, lack of breast development, diminution of axillary and pubic hair and short stature. (Patients with Turner's syndrome also have webbing of the neck, a wide carrying angle of the arms and sometimes coarctation of the aorta or other congenital anomalies.) In postpubertal ovarian insufficiency, amenorrhea and sterility are often the only manifestations, but there tends to be a gradual atrophy of the sex organs and a loss of the secondary sex characteristics without a regression to the immature state. In the menopause, such atrophic changes are usually associated with mild facial hirsutism. Occasionally, extensive hyperkeratosis on the palms and soles (keratoderma climactericum) also occurs in postmenopausal women.

When *excess androgenic hormone* is present in the developing female fetus (as in the adrenogenital syndrome), pseudohermaphroditism results, with hypertrophy of the clitoris, enlargement and often fusion of the labia majora and usually a single external urogenital orifice at the base of the hypertrophied clitoris. When virilism has its onset in the female child after birth, the external genitalia are normally formed, but the clitoris hypertrophies, somatic growth is accelerated, body contours become masculine and breasts do not develop. In the adult female, the breasts have already appeared, and virilism is manifest chiefly by hirsutism, acne, clitoral hypertrophy and the gradual assumption of a male habitus.

An excess of estrogen in the female child or excess androgen in the male child results in precocious puberty. When gonadal hyperfunction begins after puberty, there are usually no changes in the external genitalia or secondary sexual characteristics (except menorrhagia in the female). If brown pigmented spots with very irregular ("coast of Maine") margins are found in a female with precocious puberty, a diagnosis of Albright's syndrome can be made; polyostotic fibrous dysplasia is usually associated.

Pregnancy may produce a variety of cutaneous changes, of which the most common are spider angiomas and abdominal

striae. Occasionally there is a paradoxical acne or hirsutism. Chloasma, or irregular melanotic patches, may appear, especially on the face and chest. The enlargement and darkening of the nipples and areolae during pregnancy is only partially reversed after delivery. Pruritus and other dermatoses, especially dermatitis herpetiformis, may be quite severe during pregnancy.

PITUITARY DISORDERS.—Pituitary insufficiency is marked by a soft smooth pale yellow skin, sparse hair and axillary and pubic alopecia. In acromegaly, the skin becomes coarse and thickened, individual hairs are thickened (coarse hypertrichosis), and there is hyperplasia of the sebaceous glands. The nails are often thickened and dystrophic. Macroglossia and enlargement of the bones of face, hands and feet are striking features.

METABOLIC DISORDERS

PORPHYRIA.—In the rare congenital (erythropoietic) porphyria, with hemolytic anemia and splenomegaly, excess deposits of porphyrin in the skin lead to marked photosensitization. The earliest lesions are blisters (hydroa aestivale) on skin surfaces exposed to light; later, scarring and mutilation occur. Porphyrin deposits in the teeth may give them a reddish brown appearance. The more common acute intermittent (hepatic) porphyria is manifest chiefly by abdominal pain and neurologic symptoms, and there are usually no external signs. In the cutanea tarda type of porphyria, photosensitivity develops in adult life and mutilation is less striking. Hirsutism, a ruddy violaceous complexion, brownish pigmentation and bullous lesions may occur. In several patients, red or gray hair has darkened toward a black color (10).

HEMOCHROMATOSIS.—Excess skin pigmentation is one of the most consistent features of hemochromatosis. The skin assumes a dirty gray-brown color, due to a combination of hemosiderin and melanin. Pigmentation is generalized, but most prominent on the extensor aspects of the forearms, hands and lower legs and also in the groins and axillae. Dry skin and loss of body hair are also common findings.

GASTROINTESTINAL DISORDERS

There are numerous external signs which point to the existence of underlying disease in the gastrointestinal tract. Perhaps

most common is jaundice, which may be a clue to liver disease or to extrahepatic biliary obstruction. The appearance of spider angiomas and palmar erythema may be related to increased circulating estrogen levels in patients with parenchymal hepatic dysfunction. Parotid enlargement and Dupuytren's contracture have recently been described as frequent findings in patients with cirrhosis (42, 55). Both pruritus and cutaneous xanthomas may occur as sequelae of biliary obstruction.

Occasionally there are external clues to the diagnosis of dysphagia due to *esophageal disease*. In Plummer-Vinson syndrome (iron deficiency anemia and dysphagia in middle-aged women with esophageal webs), koilonychia and angular stomatitis may occur, as in any severe iron deficiency state. Scleroderma of the esophagus may be suggested by the finding of the typical smooth atrophic skin, sometimes with pigmentary changes and telangiectasia, calcium deposits and arthritic involvement.

Patients with sprue and other severe *malabsorptive states* are likely to develop increased melanin pigmentation and the signs of vitamin deficiency or of hypoproteinemic edema. The rare entity of Whipple's disease may be suggested by the finding of lymphadenopathy and polyarthritis in a patient with malabsorption.

There are at least three interesting and distinct *intestinal polyposis syndromes* with characteristic external signs. Best known is the syndrome of generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits (29).* The characteristic small flat very dark spots occur most frequently on the lower lips and on the buccal mucosa and more rarely on the fingers and toes. The polyps are multiple and are found in the small intestine in nearly all cases, but occasionally they occur in the colon, rectum or stomach. Bleeding is the most common clinical manifestation, and colic due to intussusception is not infrequent. The hereditary nature of the syndrome is often evident and is controlled by a pleotrophic dominant gene.

Familial polyposis of the colon usually occurs without extraintestinal signs. However, Gardner has described a rare syndrome of colonic polyposis in association with multiple subcutaneous sebaceous cysts, benign osteomas of the skull or mandible, and occasionally fibromas, including incisional desmoids. Not all the various features are present in every patient with the

*[Commonly known as the Peutz-Jeghers syndrome.—Ed.]

syndrome. A pleiotropic dominant gene is apparently responsible (25).

A third syndrome, recently described by Cronkhite and Canada (15), is generalized intestinal polyposis in association with alopecia, diffuse increase in skin pigmentation and atrophy or loss of fingernails and toenails. Since virtually the entire gastrointestinal tract is replaced by polyps, it has been postulated that the ectodermal changes may be secondary to malabsorption and malnutrition.

There are a number of external manifestations of *ulcerative colitis*. Erythema nodosum has been mentioned previously. Clubbing of the fingers may occur with this disease as well as with regional enteritis. Uveitis and symmetrical arthritis are among the findings that occasionally suggest a relationship to generalized connective tissue or "collagen" disease. *Pyoderma gangrenosum* is the most specific lesion associated with ulcerative colitis, although it is occasionally seen with other debilitating states. The lesions begin as groups of pustules which enlarge, coalesce, break down and finally ulcerate. They are often multiple, occur mainly on the lower extremities, and have slightly raised, bluish edematous and undermined borders. Other skin lesions which occur with increased frequency in ulcerative colitis are furuncles and carbuncles, aphthous stomatitis and urticaria.

Acrodermatitis enteropathica is a rare condition of infants and young children characterized by extensive areas of erythema and exudation around the mouth and anus and also on the hands and feet, in association with severe diarrhea and total alopecia (19). Physical and mental retardation frequently result. Most cases show severe dystrophic changes in the nails. Although partial remissions occur, the over-all course of the untreated cases is usually progressively downhill, resulting in death in early childhood. Monilia organisms have been cultured from the stools in many cases, but they are generally believed to be secondary invaders. The etiology of the disease remains a mystery.

The striking cutaneous manifestations of metastatic carcinoid tumors and the nonspecific signs of gastrointestinal malignancy are discussed in the section on neoplastic disease.

GASTROINTESTINAL BLEEDING.—Many of the external clues to the diagnosis of gastrointestinal hemorrhage are discussed elsewhere in this review. Jaundice, spider angiomas and palmar erythema may suggest *cirrhosis* and esophageal varices. A num-

ber of *vascular lesions* may be present both on the skin and in the gastrointestinal tract; examples are hereditary hemorrhagic telangiectasia, generalized telangiectasia, radiation telangiectasia and the bluish vascular nevi described by Bean (3). The *purpuras* are occasionally important as causes of gastrointestinal bleeding; examples are: thrombocytopenia, scurvy and Schönlein-Henoch or other vascular purpuras. The various *intestinal polyposis* syndromes have been described previously. The *gastrointestinal neoplasms* which give rise to external manifestations may also be sources of hemorrhage. Kaposi's angiosarcoma deserves special mention in this regard, since, although the vascular tumors are rare, they are quite likely to bleed.

Pseudoxanthoma elasticum may present as recurrent gastrointestinal hemorrhage. The basic defect appears to be a hereditary weakness of collagen fibers, which leads to degenerative "elastoid" changes in areas under stress. Involvement of muscular arteries causes hypertension, peripheral calcification and hemorrhage from the stomach or bowel. Occasionally bleeding occurs from the uterus, nose or other sites. The disease may be recognized by the characteristic yellowish pink papular thickenings which give a crepelike appearance to the skin, especially over the neck, axillae and groins, or by the angioid streaks in the optic fundi (35).

Another rare cause of gastrointestinal bleeding is *primary systemic amyloidosis*. The diagnosis may be suspected by the finding of macroglossia or by the appearance of hard translucent plaques or nodules in the skin, especially on the face, neck and trunk. Cutaneous hemorrhages are also common.

Connective Tissue Disorders

Some of the most striking of the varied expressions of the "collagen diseases" are their external manifestations (11). Recognition of these external signs may, on occasion, point to the explanation for pathology in the cardiovascular, gastrointestinal, hematologic or nervous systems, as well as in kidney, joints and serous membranes.

The classic cutaneous sign of *systemic lupus erythematosus* is dilatation of minute vessels, resulting in patchy erythema in the "butterfly area" of the cheeks and bridge of the nose, sometimes spreading to the neck, upper thorax and arms. Edema, diffuse erythema and erythematous macules are also common.

Characteristically, the lesions are exacerbated by exposure to sunlight. Loss of hair is not infrequent, but hyperkeratosis and plugging of follicles is less evident than in discoid lupus. Petechial hemorrhages and purpura may occur in patients with thrombocytopenia.

In *rheumatoid arthritis,* the most specific pathologic lesions are the subcutaneous nodules, which occur in at least one fourth of patients at some time during their illness. The nodules are usually 1 or 2 cm. in diameter and are most common over bony prominences, especially the ulnar aspect of the forearms, near the olecranon process. These nodules are usually firm, freely movable and nontender, and they persist for months or years. Histologically, the nodule consists of a central zone of fibrinoid necrosis surrounded by a zone of histiocytes and lymphocytes and by a peripheral zone of granulation tissue and fibrosis. Similar nodules are occasionally seen in lupus erythematosus.

Excessive sweating of the hands and feet and palmar erythema are very common in rheumatoid arthritis. Pleomorphic erythematous eruptions are also frequent, especially in children. Muscle atrophy is common, even in early cases. Atrophy of skin occurs in many patients and may be associated with dystrophic changes in the nails. Psoriasis occurs with increased frequency in patients with rheumatoid spondylitis, as well as in rheumatoid arthritis. Ocular complications include uveitis, episcleritis and keratoconjunctivitis sicca.

In *rheumatic fever,* erythema marginatum is the most characteristic lesion, although it occurs in only about 10% of the patients with the disease. Other cutaneous manifestations include other types of erythema multiforme, pallor and purpura. The subcutaneous nodules of rheumatic fever are usually smaller than those of rheumatoid arthritis; and they occur in clusters adjacent or attached to tendons and ligaments, especially on the extensor surface of wrists, elbows and knees, on the back of head and over the vertebral spines. Occasionally they occur in the skin itself. As with rheumatoid nodules, their localization suggests a relationship to trauma. They differ from rheumatoid nodules in that they are transient, lasting at most a few weeks, and in that, histologically, necrosis and fibrosis are minimal. All the cutaneous manifestations of rheumatic fever are comparatively rare in adults.

Scleroderma is characterized by edema and swelling of subcutaneous tissue, which progresses to fibrosis and atrophy, with resultant restriction of movement. Typically, the lesions begin

and are most marked in the face and the hands; later they may involve the neck, shoulders, trunk and lower extremities. *Poikiloderma atrophicans vasculare* is a mixture of mottled pigmentation, atrophy and telangiectasia which may occur in normal persons but is frequently associated with scleroderma or dermatomyositis. Interstitial calcinosis may also occur in either disease. Raynaud's phenomenon may occur in any of the collagen diseases except rheumatic fever.

Dermatomyositis is marked by edema, erythema or violaceous rashes involving the face, neck, trunk and upper extremities; periorbital lesions are especially common. The myositis is manifested initially by swelling and tenderness and later by atrophy of striated muscles of the trunk and proximal portions of the extremities.

In *periarteritis nodosa,* multiple small tender erythematous subcutaneous nodules may occur; classically, though infrequently, they are found along the course of small arteries. Any of a variety of nonspecific eruptions may occur, including urticaria, purpura and erythema multiforme. In severe cases, hemorrhagic vesiculobullous lesions or focal areas of necrosis and ulceration may be present.

Neurologic Disorders

A special term, the *phakomatoses,* has been used to refer to the neurologic disorders characterized by the presence of external (and retinal) stigmas or spots (4). Most common is *neurofibromatosis,* first described in detail by von Recklinghausen in 1882. The syndrome consists of multiple neurilemmal sheath cell tumors in the skin and subcutaneous tissue and along peripheral or cranial nerves, associated with light brown café-au-lait spots on the skin. The spots are irregular in shape with relatively smooth ("coast of California") borders, and occur mainly on the trunk. While similar lesions may be found in normal persons, a presumptive diagnosis of neurofibromatosis can be made if there are more than six café au lait spots greater than 1.5 cm. in diameter (16). On the other hand, about 5% of persons with proved neurofibromatosis have no café au lait spots. Intracranial complications of neurofibromatosis include acoustic neuromas, optic gliomas and meningiomas. Mild mental retardation is the rule, and epilepsy is present occasionally. Spinal nerve tumors may compress the cauda equina or the cord

itself, producing paralyses and sensory defects. Neurofibromas may arise in any portion of the sympathetic nervous system, including the viscera. Involvement of bones may lead to scoliosis and other deformities. About 10% of patients with pheochromocytoma also have neurofibromatosis.

The triad of *tuberous sclerosis* consists of mental deficiency, epilepsy and adenoma sebaceum. The latter are small firm, yellow-pink waxy-appearing papules in the butterfly area of the face, with hypertrophy of the sebaceous glands. In some cases there is also telangiectasia. Periungual fibromas, abnormal pigmentation and other dermatoses may be present. The brain lesions consist of multiple firm (tuberous or potato-like) sclerotic lesions of dense gliosis scattered over the surface of the cerebral cortex; calcification is often present. Any of a variety of visceral tumors may occur, often of a low-grade malignancy and asymptomatic during life; many of these are hamartomas rather than true neoplasms. Renal tumors have been found in about 60% of the patients autopsied. Rhabdomyomas of the heart are present in about 15% of the patients, and their appearance is almost entirely restricted to patients with tuberous sclerosis. Retinal tumors are also seen, and a variety of congenital malformations. Pulmonary involvement may cause diffuse miliary or cystic changes and occasionally progressive dyspnea. Death usually occurs in childhood or early adulthood of epilepsy, visceral tumors or intercurrent disease.

The vascular neurocutaneous syndromes are discussed in the section on angiomas (p. 21).

Other external lesions frequently associated with mental deficiency or epilepsy include *cutis verticis gyrata,* in which there is coarse furrowing of the scalp; *incontinentia pigmenti,* in which melanotic pigmentation is distributed in bizarre patterns of flecks and whorls; and *congenital ectodermal dysplasia,* in which there are anhidrosis and developmental defects of skin, hair, nails, teeth and sometimes the brain.

Excessive seborrhea, a common finding in patients with postencephalitic Parkinsonism, is the result of hyperplasia of the sebaceous glands. In unilateral extrapyramidal disease or in hemiplegia, the seborrhea is greater on the involved side. The pathogenesis of this interesting phenomenon is unknown.

The finding of *trophic ulcers* or of gross deformity and derangement of a joint (*Charcot's joint*) may be a clue to the presence of loss of pain sensation, as in tabes dorsalis, syringomyelia or diabetic neuropathy. A tuft of hair over the sacrum

may suggest the presence of an occult spina bifida. Finally, *herpes zoster,* while presenting as a vesicular lesion of the skin, is, of course, fundamentally the result of viral infection of a dorsal root ganglion. The systemic implications of zoster are discussed in the following section, on neoplasia.

Neoplasia

An important group of external signs are those which point to visceral malignant disease (17). Most obvious are the *cutaneous metastases* and *infiltrative lesions.* The most extensive and frequent skin metastases occur in carcinoma of the breast; they are also common in carcinoma of the lung and stomach and in malignant melanoma; and they occur occasionally with primary neoplasm in the kidney and uterus and in other sites. Skin metastases are frequently confined to the region adjacent to the primary growth, presumably on the basis of dissemination of malignant cells via lymphatics. Metastatic nodules on the scalp are especially common in carcinoma of the breast.

Infiltrative lesions are most common in monocytic and chronic lymphocytic leukemia. They also occur in other leukemias and the lymphomas, and occasionally in Hodgkin's disease. Usually there is evidence of involvement of blood, bone marrow or lymph nodes, but rarely the first manifestation is in the skin. In *mycosis fungoides* the skin is the primary site; pruritic scaling erythematous eruptions are succeeded by infiltrated plaques and finally tumors, which may eventually ulcerate. Death may occur before involvement of blood or lymph nodes is manifest (6, 31).

Probably the most common external manifestation of cancer is *pallor,* a reflection of the associated anemia. When the anemia results from blood loss, as with a bleeding gastrointestinal lesion, the neoplasm may still be surgically resectable. However, the nonspecific anemia of cancer, resulting from a combination of accelerated destruction and inadequate production of red cells, is frequently associated with disseminated and incurable disease.

Purpura should also alert the physician to the possibility of malignant disease. The petechiae or spontaneous ecchymoses of thrombocytopenia are frequent heralds of acute leukemia, but they are also seen in the chronic leukemias and occasionally in lymphomas and metastatic carcinoma when there is extensive invasion of the bone marrow. Large ecchymoses may occur in

carcinoma of the pancreas or liver as a result of impaired synthesis of proconvertin, prothrombin and other clotting factors. Severe generalized purpura may be due to the abnormal fibrinolytic activity occasionally seen with carcinoma of the pancreas or prostate.

Generalized pruritus (without cutaneous infiltration) as a sign of neoplasia is most common in Hodgkin's disease and in the obstructive jaundice of carcinoma of the head of the pancreas or the ampulla of Vater. Pruritus occurs in about 20% of the patients with Hodgkin's disease; at times it is extremely severe and incapacitating, and it may be the initial and major manifestation of an exacerbation of the disease (6, 31). Occasionally pruritus occurs with chronic leukemia or lymphoma or with carcinoma of the stomach, breast or ovary, especially when metastatic (43). Usually the itching occurs in the absence of visible cutaneous lesions; however, at times there are papular eruptions (prurigo) and, rarely, generalized urticaria, especially with Hodgkin's disease or gastrointestinal malignancy.

A much more unusual manifestation of Hodgkin's disease is *acquired ichthyosis*. The lesions are generalized in distribution and wax and wane with the activity of the underlying disease and its response to therapy. Biopsy shows only the usual hyperkeratosis of ichthyotic skin.

Herpes zoster is seen occasionally in patients with Hodgkin's disease and the lymphomas, and rarely with chronic lymphocytic leukemia or metastatic carcinoma of the breast. The segment involved frequently corresponds to the site of neoplastic involvement.

Generalized erythroderma is occasionally the initial manifestation of chronic lymphatic leukemia or Hodgkin's disease and is rarely a clue to the presence of a visceral carcinoma. In the latter situation, the lesions are usually nonspecific; but in the case of leukemia, there may be extensive lymphocytic infiltration of the skin.

Abnormal pigmentation is a frequent finding in patients with neoplastic disease. Most common is jaundice, which usually results from either intrahepatic or extrahepatic biliary obstruction. A diffuse increase in melanin deposits in the skin occurs occasionally in Hodgkin's disease, visceral carcinomas and chronic myelogenous leukemia. Melanoderma may also result from antileukemic chemotherapy, particularly the alkylating agents.

A special and fascinating variety of melanin pigmentation is

acanthosis nigricans (18). The lesions are patchy areas of deeply melanized irregular thickening of the skin, which forms a rough verrucous surface, sometimes studded with papillomatous vegetations. Acanthosis nigricans is symmetrical, most common in the axillae, neck and groin, but may occur elsewhere. Any adult who has recently developed this dermatosis should be suspected of having an internal adenocarcinoma. In about 90% of cases, the tumor is intra-abdominal, usually gastric in origin. Primaries in the breast and lung have also been reported. Thus far, the mortality rate of patients with acanthosis nigricans has been 100%, even though there is not always evidence of metastasis when the skin lesion is discovered. If the internal tumor is irradiated or excised, the dermatosis (which is histologically benign) subsides and may even disappear; when the cancer recurs, the skin lesion reappears or increases in extent. The mechanism of acanthosis nigricans is not well understood, but stimulation of the dermatosis by substances elaborated by the tumor has been suggested. The acanthosis nigricans which rarely occurs in children is not associated with malignancy, nor is the pseudoacanthosis nigricans of obese brunette persons of any age (18).

The syndrome of melanin spots of oral mucosa, lips and digits and of generalized intestinal polyposis has been discussed previously. The question of malignant change of the intestinal polyps has not been settled. Histologic changes in the polyps suggesting a precancerous lesion may instead represent a developmental anomaly similar in nature to hamartomas (2). However, the polyposis of the Gardner syndrome, associated with soft-tissue neoplasms and osteomas, involves chiefly the colon and is much more likely to evolve into carcinoma, as in at least 8 of the 13 patients in the original family studied by Gardner (25).

Recurrent thrombophlebitis in the absence of predisposing venous disease is occasionally a clue to the presence of a visceral carcinoma, although the majority of patients with migratory thrombophlebitis do not prove to have cancer. In Edwards' series of 29 cases of migratory thrombophlebitis that were associated with carcinoma (20), the primary lesion was in the body or tail of the pancreas in 16 cases, the stomach and lung in 4 cases each, the gallbladder in 3, and there was an undetermined primary site in 3 cases. The cause of the phlebitis is unknown, but it has been suggested that the tumor produces enzymes capable of damaging the venous endothelium.

Perhaps the most familiar of the peripheral signs of internal neoplasia is *hypertrophic osteoarthropathy* or its minor variant, *clubbing of the fingers*. As noted above, bronchiogenic carcinoma is only one of several common causes for this finding. When hypertrophic osteoarthropathy is associated with great thickening of the skin, especially of the palms and the face, including scalp, ears and lips, pachydermoperiostitis is said to exist. There is accentuation of the folds in the forehead, with deep horizontal furrows and shiny skin; and macroglossia is often present. Pachydermoperiostitis rarely results from causes other than carcinoma of the lung.

Dermatomyositis is associated with malignant disease in 10 or 15% of the cases (54). Among males, the primary neoplasms are most often in the stomach or lung; among females, most often in the breast or ovaries. In many of the reported cases, the dermatomyositis has preceded recognition of the tumor. Surgery or radiation therapy of the tumor is often followed by improvement of the dermatomyositis; however, recurrence of the neoplasm does not usually lead to exacerbation of dermatomyositis. It is of interest that in children with dermatomyositis, no such association with malignancy has been found.

There are a variety of *neurologic manifestations* of visceral carcinoma. Brain and Henson (9) have distinguished five patterns of "carcinomatous neuromyopathy": (1) cortical cerebellar degeneration, with vertigo, ataxia, coordination defects and prominent mental changes; (2) neuromuscular disorders, chiefly proximal muscle weakness; (3) a mixed form, with muscle wasting and weakness, bulbar and oculomotor weakness and minor cerebellar involvement; (4) a sensory neuropathy, with pains and dysesthesias in the extremities, sometimes progressing to total sensory loss; and (5) a sensorimotor form, sometimes with abnormal reflexes. In any of these syndromes, mental changes may occur, and occasionally progressive dementia may dominate the picture. The primary neoplasm was in the lung in 32 of the 42 patients in Brain and Henson's series; primary neoplasms have also been found in the ovary, prostate, rectum and breast. There is no relationship between the size of the tumor and the severity of neurologic disease. Removal of the tumor is usually without effect on the neurologic symptoms (9).

Recently the unique syndrome of *metastatic carcinoid* tumors has been delineated (46). Appendiceal carcinoids are nearly always benign, while ileal and the rare bronchial carcinoids (51) usually possess a low-grade malignancy. About half of

these carcinoids are functional and produce serotonin, which is a potent vasomotor and smooth-muscle stimulant and accounts for the characteristic signs and symptoms. The earliest and most characteristic manifestation is paroxysmal flushing of the skin, especially of the face and neck, with patches of purple cyanosis alternating with areas of pallor and others of deep erythema. Other features of the attacks are hyperperistalsis, with watery diarrhea and wheezing respirations. After several years, gross telangiectasia develops and the patient assumes a plethoric appearance. Valvular deformities may result in pulmonary stenosis and tricuspid insufficiency and the appearance of congestive failure. Occasionally the abnormal tryptophane metabolism may contribute to the development of the signs and symptoms of pellagra.

Virtually any type of *erythema multiforme*—macular, papular or bullous—may occur in association with internal tumors. Frequently the appearance of the skin lesion follows radiation therapy to the neoplasm, suggesting that the reaction may be due to disintegrating tissue.

Erythema gyratum repens, a constantly changing eruption, occurs over the trunk and extremities in irregular wavy bands resembling the grain of cut pine. The lesion is rare but usually occurs in association with anaplastic carcinomas of the breast or lung. *Dermatitis herpetiformis* may occur with any malignancy, but particularly with tumors of the ovary and thyroid, especially when there is necrosis in the primary tumor.

Kaposi's sarcoma is a relatively benign, slowly progressive angiosarcoma, characterized by bluish purple pigmented hemorrhagic plaques and nodules, mainly on the lower extremities. Visceral angiosarcomas occur in about 10% of the patients. Cardiac involvement may cause pericardial effusion, heart block, arrhythmia or congestive failure; right atrial tumors have caused sudden death by ball valve obstruction. In the gastrointestinal tract, lesions may cause symptoms on a mechanical basis. The mesenteric lymph nodes, lungs, liver and central nervous system may also be involved. Occasionally the lesions undergo malignant degeneration, either in the extremities or the viscera. There is also a high incidence of diabetes mellitus.

Other dermatoses associated with visceral malignancy include Bowen's disease (multiple epidermoid carcinoma in situ of the skin), in which a high incidence of internal cancer of all types has been reported; and tuberous sclerosis, in which renal

carcinomas and rhabdomyomas of the heart are particularly common.

Reactions to Drugs and Toxic Agents

Reactions to chemical agents may result from allergic or immunologic mechanisms, from idiosyncratic but nonallergic hypersensitivity or from excessive dosage in a normal person. The most common cutaneous allergic reactions to drugs are urticaria and maculopapular erythemas; these are typical of many of the reactions to penicillin, the barbiturates and the antithyroid compounds. Erythema multiforme and erythema nodosum occasionally follow the administration of certain drugs, such as the sulfonamides. More severe allergic reactions may be characterized by purpura, exfoliative dermatitis or periarteritis nodosa. Fixed drug eruptions, recurring in the same location on the readministration of the offending agent, may be seen with phenolphthalein, barbiturates and other drugs.

Most of the above reactions are quite nonspecific. However, the iodides and bromides characteristically give rise to pustular lesions resembling acne. Particularly with iodide, nonallergic idiosyncrasy seems to predispose to the development of these lesions. The prolonged ingestion of bromide may also cause peculiar vegetative lesions on the shins.

Another specific lesion is that of arsenic intoxication. This is characterized by dry scaly desquamation and fine spotty "raindrop" hyperpigmentation of the skin over trunk and extremities, with wartlike brownish hyperkeratotic lesions, especially on the palms and soles.

The therapeutic use of silver compounds may result in the grayish blue skin discoloration of argyria. This may be readily distinguished from cyanosis by its metallic gray hue, by its persistence in the skin when blood is expressed by external pressure and by the usual absence of associated cardiac or pulmonary disease. Similar metallic discolorations rarely occur as a result of the use of gold, bismuth or mercury. Another heavy metal, thallium, is notable for the alopecia which follows toxic exposure.

A few drugs have the propensity for occasionally producing jaundice on a toxic basis, most often as a result of cholestasis and obstructive liver damage. This subject is well documented in the literature.

Finally, Cushing's syndrome must be mentioned as an increasingly common and easily recognized manifestation of prolonged therapy with corticosteroid hormone preparations.

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